ENTERAL FEEDING METHODS AND SURGICAL COMPLICATIONS IN CHILDREN

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Declaration

I, Rashmi Roshan Singh, confirm that the work presented in this thesis is my own. I have conducted and co-ordinated the randomised controlled trial and retrospective studies. Dr Simon Eaton has provided support in analysing the results and performed the statistical analysis. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Background

In the unwell child who is unable to feed orally, various methods for enteral feeding having been advocated. The ideal method for a particular child has to be tailored according to his/her anatomy, physiology and requirements. The impact of complex medical background on outcomes and complications following a surgical procedure in children remains largely unrecognized.

Aims

1. To determine whether percutaneous endoscopic gastrostomy (PEG) is superior to radiologically inserted gastrostomy (RIG)
2. To determine outcomes following surgical jejunostomy (SJ) or radiologically inserted gastro-jejunal (RGJ) tube
3. To study complications after surgery and determine its effect

Methods

A double-blinded randomised controlled trial was conducted in children needing gastric feeding, who received either a PEG or RIG. They were followed up for up to 3 years to record any complication.

Retrospective reviews of buried bumpers (a specific complication of gastrostomy), and the nutritional outcomes following jejunostomy placement (SJ or RGJ) was carried out.

Available scoring systems for post-operative complications were reviewed and initial development of a new paediatric complexity scoring system was performed.

Results

In the trial 198 children were randomised (100 PEG and 98 RIG). They were followed up to a median of 1 year (6 weeks to 3 years). There was no difference between total number of complications or the rate of complications, following PEG or RIG.

Both SJ and RGJ are able to maintain and improve growth in a carefully selected group of children.

There is a need for validation of a developed paediatric complexity scoring system.

Conclusions

PEG and RIG have equivalent rates of complications.

SJ and RGJ cannot be compared as they are used for patients at different stages in a spectrum of malnutrition.

Impact of the complexity of paediatric patients on their post-operative complications needs thorough consideration to improve outcomes.

Impact Statement

PEG vs. RIG Trial

The major work in this thesis is a randomised controlled trial of percutaneous endoscopic gastrostomy (PEG) versus radiologically inserted gastrostomy (RIG). In a retrospective study, RIG was found to have more complications than PEG, suggesting that RIG should not be performed. However, the double blinded randomised control trial performed and analysed in this thesis found no difference in number or rate of complications following PEG or RIG. This has important impact on centres practising both methods of gastrostomy insertion, leading to streamlining of patient treatment to the more readily available option without any concerns about difference in outcomes. Further study of this cohort of patients can provide information about the development of gastro-oesophageal reflux, need for further feeding device or resolution of symptoms and establishment of oral feeding.

The publication of the trial in British Journal of Surgery (2017;104(12): 1620-1627), will further disseminate and provide robust, scientific evidence about the efficacy of PEG and RIG.

Buried bumper

This is a major, life threatening complication after a gastrostomy. I reviewed this complication in a large cohort of children. I realised that the design of the gastrostomy and care are major contributing factors for developing a buried bumper. I have recommended maintaining a prospective registry and changing a bumper gastrostomy device to a balloon gastrostomy sooner.

The publication of the findings in European Journal of Pediatric Surgery (2013; 23(1):76-79), has increased awareness and provided management options to clinicians and parents.

Jejunal feeding

Jejunal feeding for children unable to tolerate gastric feeds can be achieved by surgical jejunostomy (SJ) feeding tube or radiologically inserted gastro-jejunal (RGJ) feeding tube. I reviewed complications and nutritional outcomes following jejunostomy placement (SJ or RGJ). I have reviewed different factors i.e. patient's medical background, practicality of caring for the device, local resources available and complications. The review published (Pediatric Surgery International 2018; 34(9):951-956), will provide information to families while they are being counselled for the choice of jejunal tube. They should be able to make an informed decision along with the clinician.

I have recommended a prospective randomised controlled trial, with a sample size to detect a difference in complications/outcomes after anti-reflux operation or gastro-jejunal tube feeding in neurologically impaired children. A formal quality of life assessment for the patient and caregivers is also needed.

Complication Scoring

Reporting of complications in children is not standardised. The adult complication reporting systems do not account for a child's physiology and the complexities of other medical/surgical pre-existing conditions. Impact of the complexity of paediatric patients on their post-operative complications needs thorough consideration to improve outcomes. I have developed the Paediatric Complexity Index (PCI). It requires further development and extensive validation.

I have had discussions with researchers involved in developing Patient Reported Outcome Measures at Oxford for adults. With their experience, this work can be taken forward to develop a similar model in children. This requires funding and pooling of resources from clinicians (paediatric

anaesthetists, intensivists and surgeons) to non-clinicians (health economists, psychologists, statisticians and website development specialist).

Table of Contents

Table of Figures

Table of Tables

Acknowledgements

I am forever indebted to my supervisor Dr Simon Eaton for the guidance and support he has provided me over the last six years. He has been patient and encouraging and the voice of reasoning when I have faltered. I am extremely grateful to Mr Joe Curry, who has supported me and encouraged me with every step of my research. I am grateful to Professor Paolo De Coppi and my former supervisor Professor Agostino Pierro who were instrumental in starting my research and seeing it through. They have instilled in me the principles of research and inquisitiveness for seeking scientific reasoning for clinical problems. They have inspired me by setting high standards. I thank them for this. I would like to thank Dr Derek Roebuck, for his advice, guidance and encouragement.

I would like to thank everyone involved in the design and setting up of the PEG vs. RIG trial – especially Dr Shireen Nah.

I would like to acknowledge Miss Francesca Stedman who was equally involved in developing the Paediatric Complexity Index and completing the pilot study. We spent many a warm afternoon labouring through thick sets of patient notes, in our hugely pregnant states.

Family

My husband, Ashok Singh, has been with me at every step. He has supported me, encouraged me and blindly believed in me even when I doubted myself. He has enabled me to work and study, cared for our children and made this possible.

My sons, Aaditya and Aayush, arrived just as I finished conducting the trial. It's been an incredible journey of juggling parenthood, with surgical work and completing my research. The joy and anxiety they have brought has inspired me and made me determined to complete my project. I am guilty of not enjoying the warm summer weekends with them.

I dedicate this thesis to Ashok, Aaditya and Ayush.

My parents Kiran and Shatrughna Ram, have always been there, to listen, guide and encourage me. My father-in-law Nawal Kishor Singh, who is a scientist at heart, and though a trained engineer has always shown keen interest in my project. I am grateful for their moral support and unconditional belief in me.

Mentors

My mentors in my surgical career have moulded me into the person I am today. I have imbibed their passion for surgery. They have inspired me to strive for excellence. In addition to my supervisors, I would like to mention Professor Mark Davenport, Professor of Paediatric Surgery for his subtle encouragement towards research and surgery. Mr Harish Chandran and Mr Liam Mc Carthy, Paediatric Urologists at Birmigham Childrens' Hospital. Professor V.K.Jain, Professor of Surgery at Rajendra Medical College, Ranchi, India.

PEG vs. RIG collaborators

I am grateful to everyone who has enthusiastically supported the trial in his or her clinical area of work - Dr A Barnacle, Dr S Chippington, Dr S Stuart, Dr C Gibson, Mr E Kiely, Mr I Yardley, Mr N Hall, Miss J Stanwell and Miss K Cross.

I thank everyone who assisted with the running of the trial – Mr M Bishay, Miss E Macharia, Mr M Thyoka, Miss H Carnaghan and Mr E Hannon.

DMEC members: I thank Professor Lewis Spitz and Mr Niyi Ade-Ajayi, for critically reviewing the interim analysis and making recommendations.

Funding and Research support

I thank Great Ormond Street Children's Charity for funding the PEG vs. RIG

trial.

I gratefully acknowledge the support from Great Ormond Street Hospital NIHR Biomedical Research Centre, including support from the Somers Clinical Research Facility.

Inspiration

Finally, I would like to thank all the parents who agreed to take part in the trial. I absolutely admire their dedication and love for their children. Over the course of three years while conducting the trial, I met hundreds of parents from different cultural backgrounds of children, who were unwell due to a variety of reasons. Most children would be sick with not a good prognosis, however the parents were unanimously similar, in their attitude towards research. I salute their commitment and eagerness to improve the lives of other children by participating in the trial.

Chapter 1 Introduction

1.1 Physiology of feeding

Hunger is one of the most primitive instincts that has led to survival and evolution of a species. The sensation of *hunger* is associated with craving for food and physiological effects such as rhythmic contraction of the stomach and restlessness, causing a person to look for food. A person's *appetite* makes one desire a certain type of food thus influencing the quality of food eaten. These two mechanisms are important automatic regulatory systems to ensure adequate nutritional supply for the body. However, the body needs an intact ingestion and swallowing mechanism as well.

Swallowing is a complex mechanism (Figure 1-1), as the pharynx is primarily used for respiration and it is only for a few seconds that it acts as a conduit for passage of food into the stomach. Swallowing can be divided into different phases:

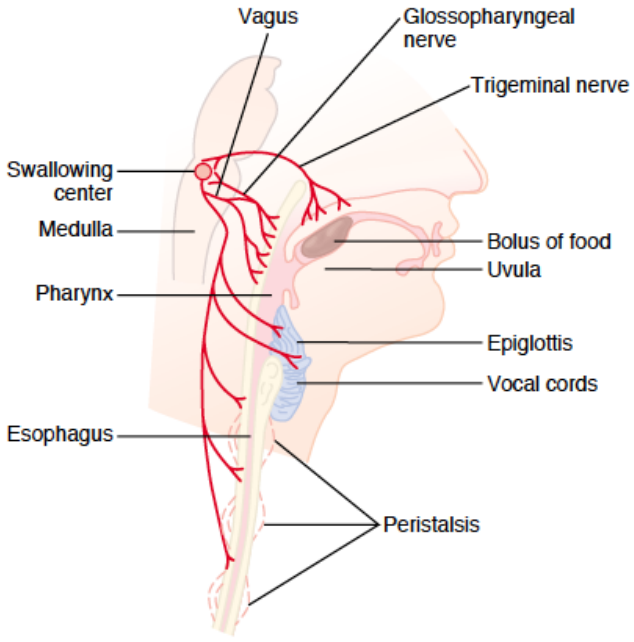

Figure 1-1 Swallowing mechanism

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1.1.1 Voluntary oral phase

This consists of the food bolus being voluntarily pushed into the pharynx by the tongue. When the food is ready to be swallowed, the tongue pushes the bolus by pressing upwards and backwards against the palate.

1.1.2 Pharyngeal phase

As the food bolus comes into contact with the highly sensitive tactile area at the back of the mouth, the swallowing reflex is initiated. The soft palate is pulled upwards closing the nasal cavity and the pharynx is pulled upwards and forwards, which together with the backward movement of the epiglottis closes the trachea for a few seconds. Sensory input via the Trigeminal and Glossopharyngeal nerves reach the *swallowing centre* in the medulla oblongata and lower pons. Motor impulses to the pharynx and upper oesophagus reach via the Trigeminal, Glossopharyngeal, Vagus and Hypoglossal nerves from the *swallowing centre*, resulting in contraction of the pharyngeal muscles and propulsion of the food bolus into the oesophagus.

1.1.3 Oesophageal phase

The peristaltic waves from the pharynx continue into the oesophagus as primary peristaltic wave propelling the food bolus downwards into the stomach. If these are not enough to push all the food that has entered the oesophagus into the stomach, then secondary peristaltic waves arise. These are partly a continuation of the primary peristaltic waves and partly a reflex initiated from the distension of the oesophagus stretching the intrinsic myenteric plexus (Arthur C Guyton, 2006).

1.2 Pathology of children needing artificial feeding

Children have an increased nutritional requirement to support their rapid growth and development. There are a number of conditions in which children

are unable to maintain an adequate nutrition and need artificial feeding/support. They can be broadly divided into two groups, due to:

i. Inadequate intake
ii. Inadequate absorption

1.2.1 Inadequate intake

Psychological – due to depressed 'hunger' or 'appetite' centre in the hypothalamus. Children with severe behavioural and gastrointestinal disorders have greatly benefitted from artificial feeding devices (Sathesh-Kumar et al., 2009, Nah et al., 2010)

Neurological - conditions such as epilepsy, encephalopathy, cerebral palsy etc. can result in uncoordinated swallowing. Due to the unsafe swallow these children have a high risk of aspiration (Sleigh et al., 2004, Townsend et al., 2008, Vernon-Roberts et al., 2010). Objective assessment of swallowing can be done using Videofluoroscopic Swallowing Study (VFSS) or Fibreoptic Endoscopic Evaluation of Swallowing (FESS). Both procdures examine the swallowing mechanism under conditions that mimic eating. The VFSS is ussually carried out by speech and language therapist and radiologist. The FESS is carried out by speech and language therapist and gastroentologist or otolaryngologist. After careful assessment, artificial feeding into the stomach with or without an anti-reflux procedure or into the jejunum is often needed.

Chemotherapy – Highly emetogenic chemotherapy results in stimulation of the Chemoreceptor trigger zone in the medulla oblongata, which in turn excites the '*vomiting'* centre (Figure 1-2). Children undergoing or due to undergo intense chemotherapy are unable to maintain adequate oral intake due to the intractable nausea and vomiting (Aquino et al., 1995, Schmitt et

al., 2012, Pedersen et al., 1999, Mathew et al., 1996).

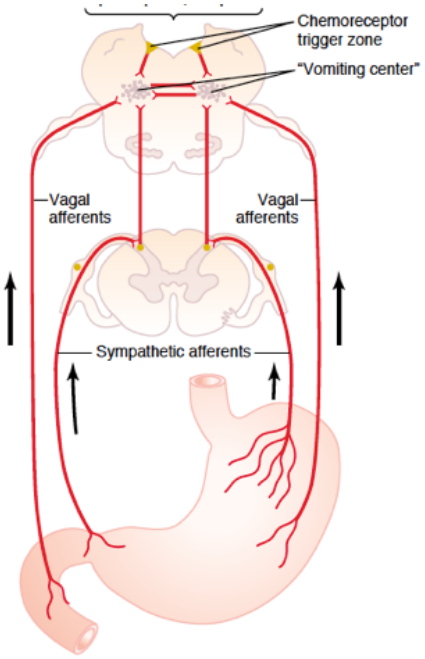

Figure 1-2 Chemoreceptor Trigger Zone and the vomiting centre in the medulla oblongata

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Increased demand - Children with metabolic disorders or renal failure require unpalatable medications or feeds in large volumes. An assisted feeing device can ensure compliance in such cases.

As a part of other surgical procedure - Children requiring a definite and secure means of enteral feed as a part of another surgical intervention such as cleft palate repair, complex cardiac surgery (Urban and Terris, 1997, Al-Attar et al., 2012).

1.2.2 Inadequate absorption

This can be due to short length of functional bowel or immature bowel or ileus as in inflammatory bowel disease, necrotizing enterocolitis, short bowel syndrome, prematurity, post major abdominal surgery.

1.3 Types of artificial feeding

1.3.1 Enteral route

The route for artificial feeding whether it is for supplementation or complete diet replacement depends on the functional status of the gastrointestinal tract, nutritional and psychological state of the patient. It is always best to use an enteral route (Figure 1-3) for nutrition if the intestine works and is of adequate length.

The commonly used enteral feeding routes are nasogastric / orogastric, nasoduodenal and nasojejunal route as short-term measures. Nasogastric tube is indicated for children with inadequate or unsafe oral intake, post operatively after major upper gastrointestinal surgery and absent gag reflex.

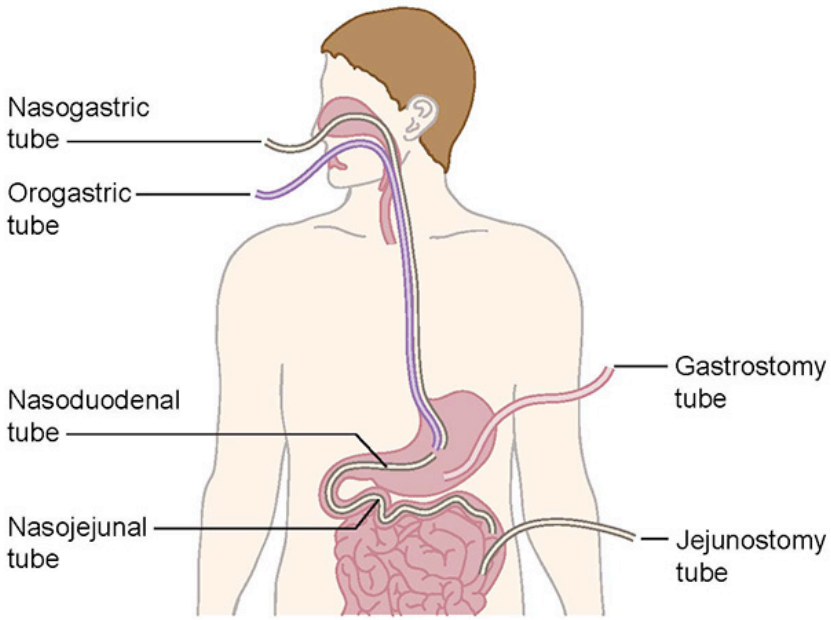

Figure 1-3 Enteral routes

(Reprinted with permission from Baxter)

Nasojejunal feeds are indicated in children with severe gastro oesophageal reflux, delayed gastric emptying and persistent vomiting. For longer term use gastric or jejunal feeding routes are preferred. The major disadvantage of

nasal route of tube feeding is that it can be pulled out by the child and lead to aspiration. In the long-term it can lead to oral food aversion.

1.3.2 Parenteral route

If the gastrointestinal tract is not functioning, then it can be bypassed and nutrients can be supplied intravenously. The administration of nutrients in high concentration requires access to a central vein. This can be through a tunnelled catheter or a sub cutaneous port into the subclavian vein (Hickman line®, Port-a-Cath) or via a central venous catheter (CVC) into the subclavian or internal jugular vein or through a peripherally inserted central catheter (PICC) into the superior vena cava (Figure 1-4, 1-5).

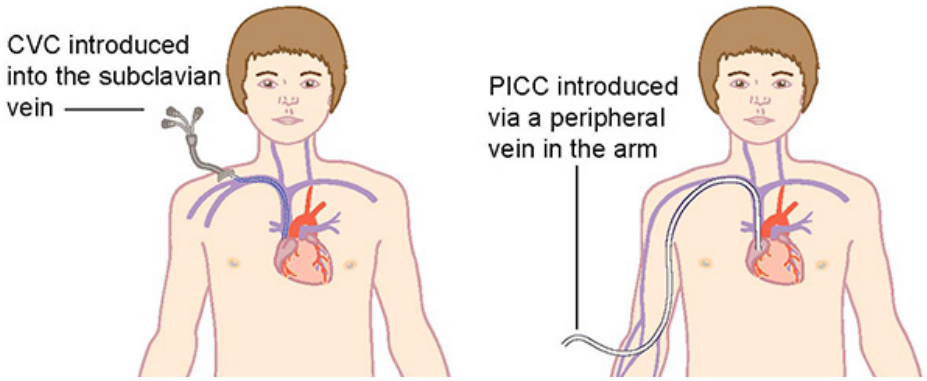

Figure 1-4 Routes of administration of parenteral nutrition

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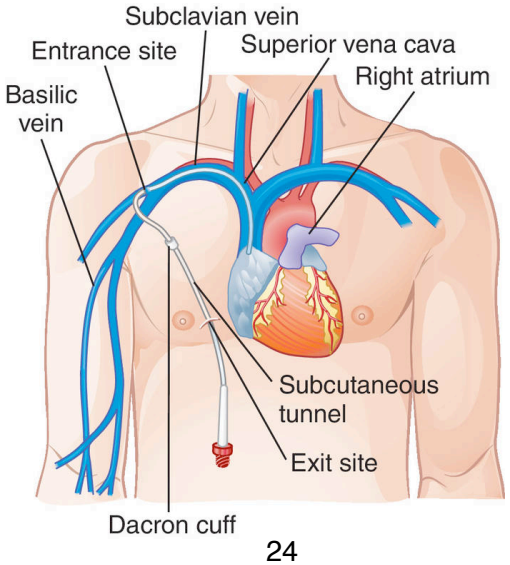

Figure 1-5 Tunnelled Hickman®/Broviac® line

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The parenteral route should not be used in the presence of an intact and functional gastrointestinal system. The disadvantages of using the parenteral route are:

i. Risk of life threatening infection
ii. Non-use of the gastrointestinal tract can lead to atrophy and loss of function
iii. Metabolic disturbances such as: hypo/hyperglycaemia, electrolyte disturbances
iv. Risk of developing fatty liver leading to liver failure
v. Cost: parenteral nutrition costs four times more than enteral nutrition

As soon as bowel function returns, children on parenteral nutrition should be weaned to enteral feeding. Even many children with Short Bowel Syndrome and enteropathy can be weaned off parenteral nutrition over time.

1.4 Description of enteral feeding methods

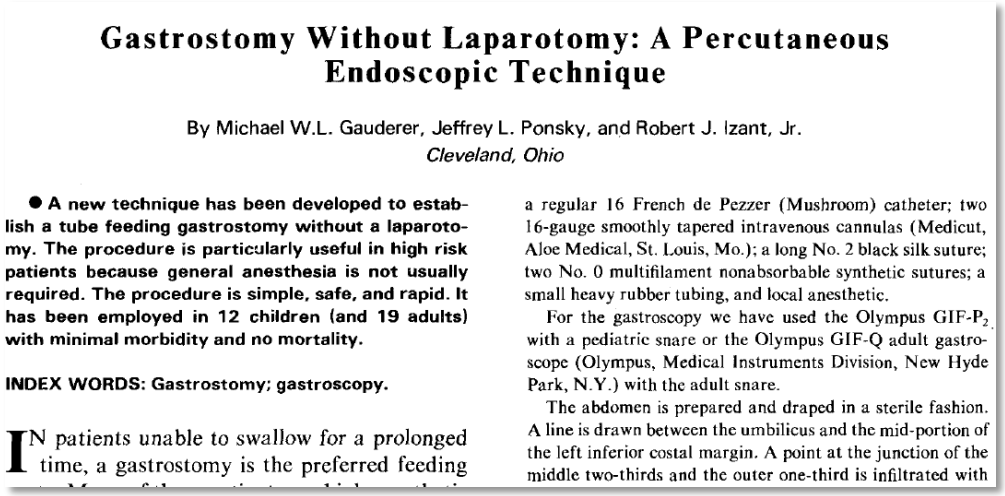
1.4.1 Naso-enteric

Nasogastric / Nasoduodenal / Nasojejunal (Figure 1-3): These are used for short term enteral feeding (usually less than 3 months). The advantage is these are easily reversible, can be inserted without a general anaesthetic and has a low cost. It does need an X-ray to confirm the position. However, the major disadvantage is that it gets inadvertently pulled out by a baby/child, which if occurs during feeds can lead to aspiration. This can lead to repeated bouts of chest infections sometimes serious enough to warrant intensive care unit admission. Long-term dependency on tube feeding is known to lead to oral food aversion (Wilken et al., 2013). The other often overlooked aspect is the social stigma associated with a tube visible on a baby's face (Avitsland et al., 2012). Some practical problems are sore anterior nares, rash on the cheek due to sticky tape and repeated attendance to the Emergency department for replacement of a pulled tube.

1.4.2 Gastrostomy

History

Gastrostomy is one of the oldest performed operations on the stomach. In 1635, Daniel Schwaben performed a gastrostomy, to remove a knife, which was swallowed by accident. It was not intended to be a gastrostomy, but a gastric fistula was formed, thus becoming a gastrostomy (Spivack, 1945). Christian A Egeberg was the first to describe gastrostomy formation in a patient with oesophageal stricture in 1837. His surgical technique was followed for a few decades (Cunha, 1946). Since then, there have been more than thirty different techniques described. New techniques were modifications to prevent the major complications of leakage, peritonitis and occasional detachment of the stomach from the abdominal wall. No technique was perfect.



Gastrostomy Without Laparotomy: A Percutaneous Endoscopic Technique

By Michael W.L. Gauderer, Jeffrey L. Ponsky, and Robert J. Izant, Jr.
Cleveland, Ohio

● A new technique has been developed to establish a tube feeding gastrostomy without a laparotomy. The procedure is particularly useful in high risk patients because general anesthesia is not usually required. The procedure is simple, safe, and rapid. It has been employed in 12 children (and 19 adults) with minimal morbidity and no mortality.

INDEX WORDS: Gastrostomy; gastroscopy.

IN patients unable to swallow for a prolonged time, a gastrostomy is the preferred feeding

a regular 16 French de Pezzer (Mushroom) catheter; two 16-gauge smoothly tapered intravenous cannulas (Medicut, Aloe Medical, St. Louis, Mo.); a long No. 2 black silk suture; two No. 0 multifilament nonabsorbable synthetic sutures; a small heavy rubber tubing, and local anesthetic.

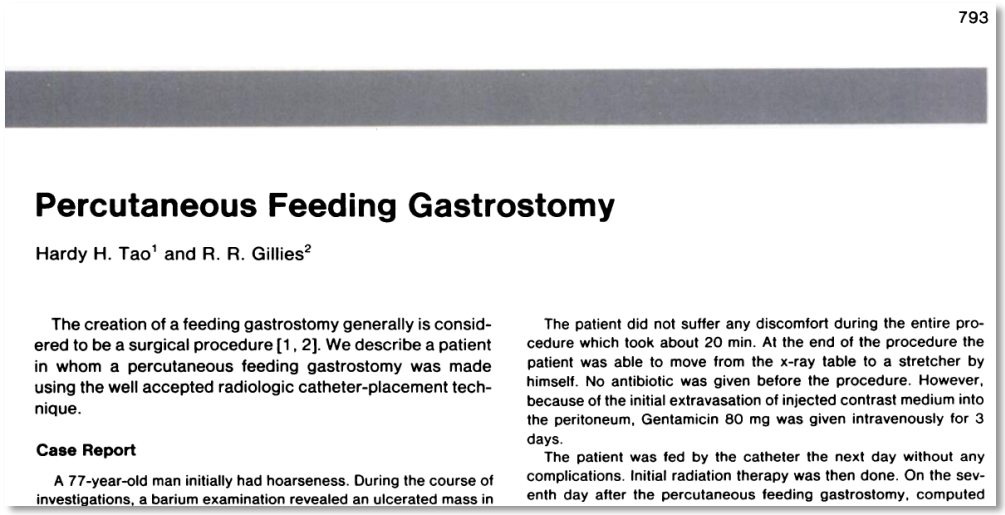
For the gastroscopy we have used the Olympus GIF-P_2 with a pediatric snare or the Olympus GIF-Q adult gastroscope (Olympus, Medical Instruments Division, New Hyde Park, N.Y.) with the adult snare.

The abdomen is prepared and draped in a sterile fashion. A line is drawn between the umbilicus and the mid-portion of the left inferior costal margin. A point at the junction of the middle two-thirds and the outer one-third is infiltrated with

Figure 1-4 Original paper describing PEG in Journal of Pediatric Surgery (Gauderer et al., 1980)

However, in 1980, Gauderer et al described percutaneous endoscopic gastrostomy (PEG), which was a major breakthrough in the evolution of this seemingly simple procedure (Gauderer et al., 1980) (Figure 1-6). He successfully performed and reported the formation of a percutaneous

endoscopic gastrostomy in twenty-six children, including two infants, one weighing 2.5kg.



793

Percutaneous Feeding Gastrostomy

Hardy H. Tao[1] and R. R. Gillies[2]

The creation of a feeding gastrostomy generally is considered to be a surgical procedure [1, 2]. We describe a patient in whom a percutaneous feeding gastrostomy was made using the well accepted radiologic catheter-placement technique.

Case Report

A 77-year-old man initially had hoarseness. During the course of investigations, a barium examination revealed an ulcerated mass in

The patient did not suffer any discomfort during the entire procedure which took about 20 min. At the end of the procedure the patient was able to move from the x-ray table to a stretcher by himself. No antibiotic was given before the procedure. However, because of the initial extravasation of injected contrast medium into the peritoneum, Gentamicin 80 mg was given intravenously for 3 days.

The patient was fed by the catheter the next day without any complications. Initial radiation therapy was then done. On the seventh day after the percutaneous feeding gastrostomy, computed

Figure 1-5 Original paper describing RIG in American Journal of Roentgenology (Tao and Gillies, 1983)

In 1983, another minimally invasive technique of radiologically inserted percutaneous gastrostomy (RIG) was introduced (Tao and Gillies, 1983, Wills and Oglesby, 1988) (Figure 1-7). Both these procedures obviated the need for a laparotomy for gastrostomy insertion. Over the last three decades it has become one of the commonest performed procedures in infants and children.

More recently, laparoscopic assisted gastrostomy tube placement has become popular. This enables visualisation of the gastrostomy device on either side of the stomach (Gauderer, 2013).

Indications

Gastrostomy is used primarily for long term feeding in infants and children. It is also used for decompression along with an anti-reflux procedure, for administration of medications and for placement of transpyloric jejunal feeding tube (Gauderer, 2013).

The three commonly used methods for gastrostomy formation are:

i. Serosa lined channel from the anterior gastric wall to the skin surface around a catheter: Stamm technique
ii. Percutaneous technique in which the introduced catheter keeps the gastric wall in apposition to the anterior abdominal wall: PEG/RIG
iii. Laparoscopically assisted technique for either of the above

Stamm gastrostomy: This involves a laparotomy and placement of purse-string sutures around the gastrostomy tube producing an invagination lined with serosa (Figure 1-8). The stomach is usually anchored to the anterior abdominal wall with sutures. The idea is to form a watertight seal around the gastrostomy.

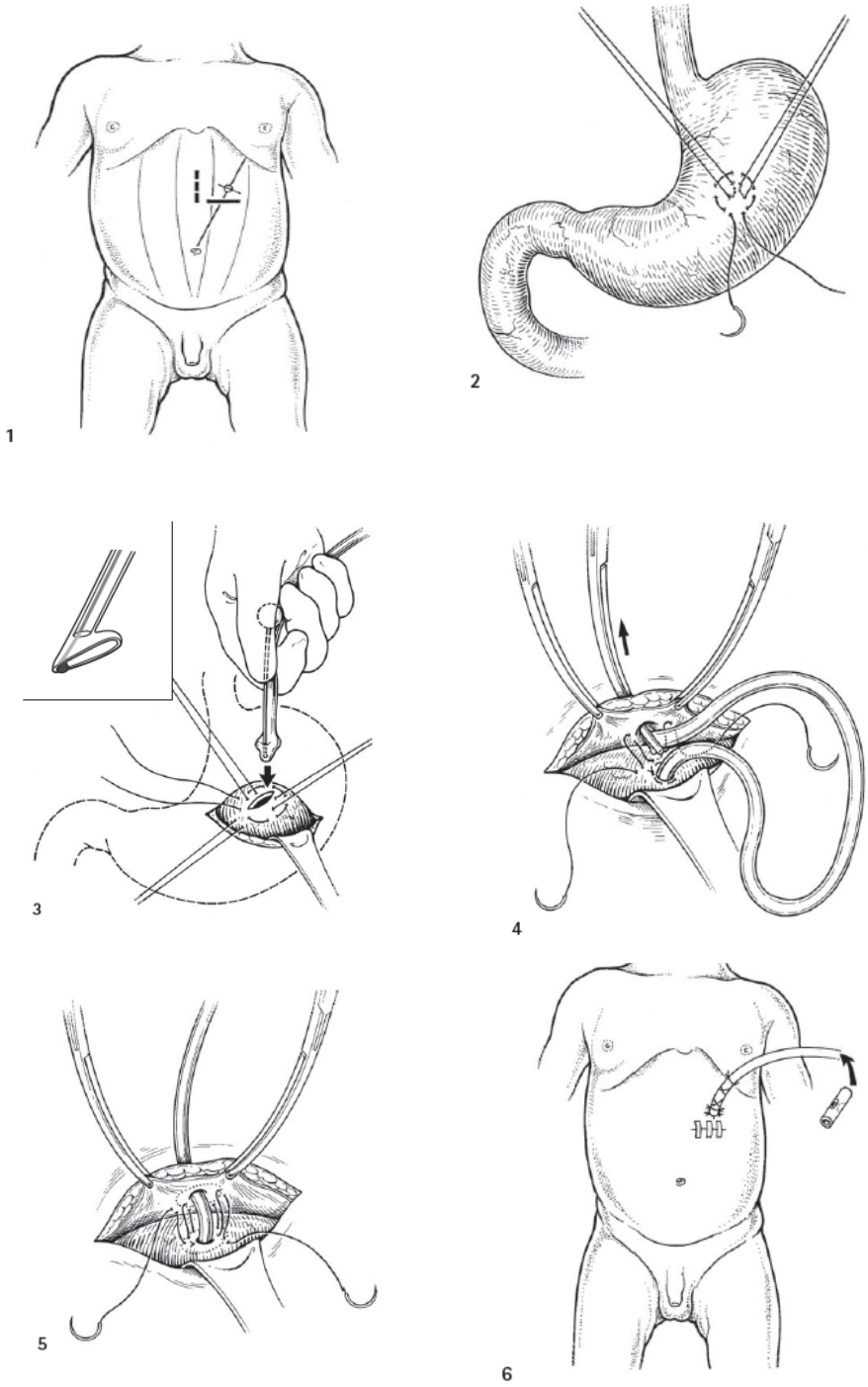


Figure 1-6 Stamm gastrostomy (Gauderer, 2013)

(Reprinted with permission from Operative Pediatric Surgery, 7th Edition CRC Press)

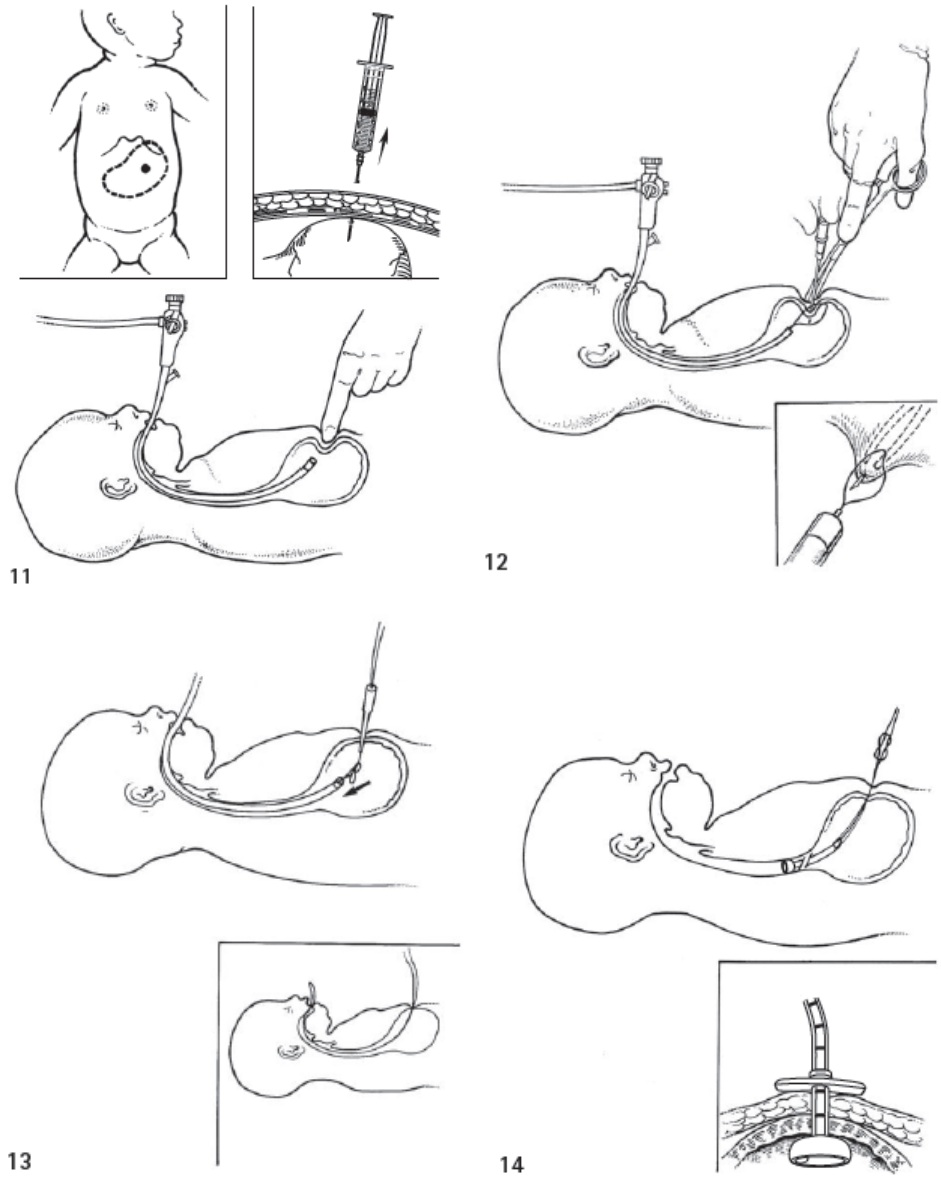


Figure 1-7 Percutaneous Endoscopic Gastrostomy

(Reprinted from Operative Pediatric Surgery, 7th Edition (Gauderer, 2013), with permission from CRC Press)

Percutaneous Endoscopic Gastrostomy ('pull' technique): In a young child this is placed under a general anaesthetic with endotracheal intubation, however in the older child/adolescent this can be placed under sedation and

local anaesthetic. After insufflation of the stomach with an endoscope, indentation of the stomach and transillumination through the abdominal wall is confirmed under endoscopic vision. A small incision is made over the area of maximum transillumination and a catheter mounted on a needle passed through followed by a guidewire. The guidewire is grasped by the endoscope, pulled out through the mouth and attached to the gastrostomy tube which is then pulled antegrade and out through the abdomen (Figure 1-9). The tube is fixed with an external fastener and no sutures placed. In children with severe scoliosis, anatomic variation of the stomach being placed cranially into the left chest is possible. The transverse colon also sits at a higher position, thereby more liable to be injured by the needle. Extreme caution should be exercised and the operator should have a low threshold to convert to open or laparoscopic assisted method (Gauderer, 2013).

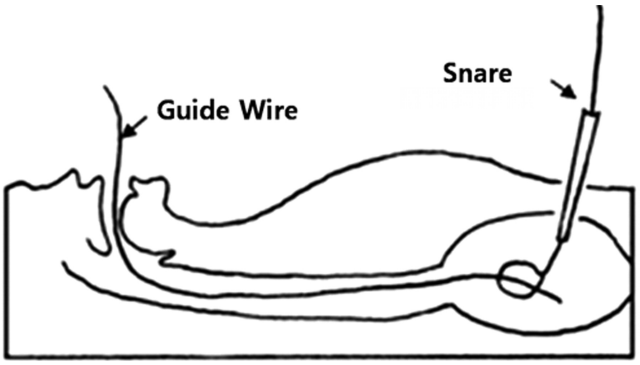


Figure 1-8 Schematic diagram of RIG placement using antegrade technique

Radiologically Inserted Gastrostomy: This can be inserted using antegrade or retrograde technique. In the antegrade technique the gastrostomy tube is pulled down the oesophagus (Figure 1-10), while in the retrograde technique it is pushed into the stomach through the anterior abdominal wall. In both techniques biplane fluoroscopy (Malden et al., 1992), with pre-placement ultrasonography for localization of the liver is used. In the antegrade technique, an orogastric snare is passed and the stomach punctured under fluoroscopic guidance with an 18-gauge trocar needle, which is used to insert

a guidewire. This is snared and withdrawn through the mouth. The snare catheter is introduced in a retrograde direction from the abdominal wall to the mouth, and the gastrostomy tube is grasped and pulled down the oesophagus.

In the retrograde technique, the stomach is punctured in the same manner, but a needle pre-loaded with a suture anchor device may be used instead of the trocar needle. These temporary retention devices help to hold the stomach in apposition against the anterior abdominal wall as the tract is dilated. A locking pigtail catheter or balloon device is then inserted. These can get displaced with more ease than a flanged device, but they are easier to remove or exchange once the tract is mature (Roebuck, 2013).

Laparoscopic assisted gastrostomy: There are several combinations of using laparoscopy for gastrostomy formation: with open (Stamm/ 'push' technique modification) or as video assisted PEG.

1.4.3 Gastro-jejunostomy

There is a high degree of foregut dysmotility in neurologically impaired children. This often results in significant gastro oesophageal reflux, which leads to failure to tolerate gastric feeding. These children can be offered a range of anti-reflux procedures. However, this is usually a major undertaking in the child with neurological impairment and decreased respiratory reserves. These children usually have a pre-existing gastrostomy and a jejunal tube through the gastrostomy may prove to be the solution (Al-Zubeidi et al., 2013). The gastro-jejunostomy is a relatively simple procedure in the hands of the radiologists and is performed without an anaesthetic. However, the trans-gastric jejunal tubes are not ideal for long-term use, as they frequently get displaced back into the stomach (Fortunato et al., 2005) and might need numerous trips to the radiology department for replacement.

1.4.4 Jejunostomy

Long-term access to the proximal small bowel for enteral feeding can be beneficial in children with neurological impairment not tolerating gastric feeds. It can also be useful in the care of children with acute surgical problems benefitting from early enteral nutrition (such as major trauma, burns, children needing long-term supplemental feeding) (Gauderer, 2012).

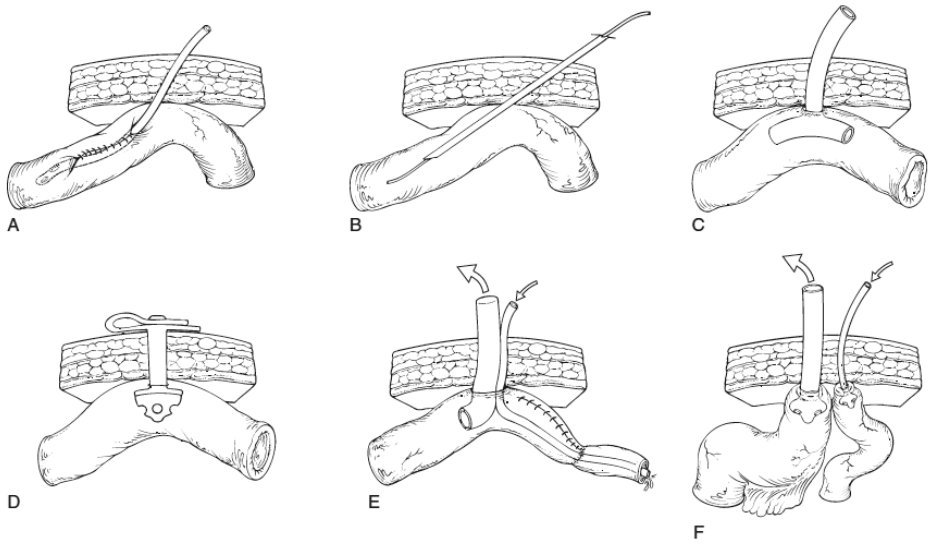


FIGURE 98-1 Diagrams of select-feeding and decompressing-feeding jejunostomies. **A,** Tunneled catheter.[9] **B,** Needle catheter. **C,** T-tube.[82] **D,** Button.[100] **E,** Proximal decompression and distal feeding across an anastomosis.[19] **F,** Temporary decompression feeding using catheters when primary anastomosis is unsafe and intestinal exteriorization is undesirable or not possible.[81]

Figure 1-9 Different types of jejunostomy

(Reprinted from Pediatric Surgery, 7th Edition(Gauderer, 2012) with permission from Elsevier Saunders)

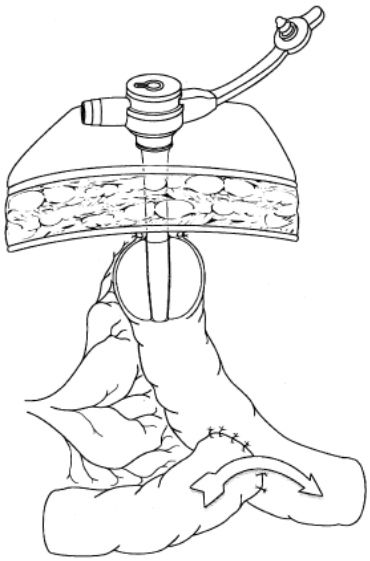


Figure 1-10 Roux-en-Y feeding jejunostomy with a balloon-type access device

(Reprinted from Pediatric Surgery, 7th Edition (Gauderer, 2012) with permission from Elsevier Saunders)

In most cases jejunostomy formation requires a laparotomy (Figure 1-11, Figure 1-12), however, in the older child percutaneous endoscopic jejunostomy (PEJ) is possible. Jejunostomies can be formed under radiological guidance by an interventional radiologist as well (Hoffer et al., 1999, Wales et al., 2002). Laparoscopy is increasingly being used for jejunostomy formation (Young et al., 2016).

1.5 Complications (literature review)

1.5.1 Gastrostomy

Since the description of PEG in 1980 (Gauderer et al., 1980), this has become the gold standard for the creation of a gastrostomy. It has obvious advantages over the 'open' gastrostomy insertion, which are less operative time, no incision therefore less pain and early establishment of feeds. However, all gastrostomies have complications. A review of the literature for complications following gastrostomy insertion is difficult. The available

studies are summarized in **Table 1-1**. The complications described as 'major' in one series might be 'minor' in another. Hence the studies are not comparable. For the purpose of uniformity in the review of series detailing complications, I have defined major complications as:

i. any complication requiring a general anaesthetic (either laparotomy or endoscopy),
ii. blood transfusion or
iii. non-prophylactic antibiotic treatment;
iv. death.

Gastro oesophageal reflux (GOR) has been included as a 'major' complication in some of the series, the argument being that the insertion of a gastrostomy alters the anatomy of the stomach, which might make GOR worse in some cases and give rise to GOR de novo as well. In children with neurological impairment and complex medical conditions, gastro oesophageal reflux disease (GORD) is a spectrum of evolving disease. The volume and speed of feeds infused also affects GOR. It is difficult to definitively establish that a gastrostomy is responsible for GOR in these children. It might well be a part of the natural history of their inherent disease, due to which there is an apparent association of GOR with gastrostomy. To this effect there are conflicting results from trials conducted in paediatric and adult patients (El-Matary, 2008). In the paediatric literature, Grunlow et al (Grunow et al., 1989) concluded that PEG insertion leads to significant GOR; while Launay et al and Wilson et al (Launay et al., 1996, Wilson et al., 2006) concluded that PEG placement does not increase GOR.

The series which have been published in the 1990s are most likely soon after the introduction of PEG technique and therefore probably have a low threshold for conversion to open procedure and may also have a higher complication rate.

Author (year of publication)	Place	Study date	n	Type of Gastrostomy	Study type	Major Complications	Death
Gauderer (1991)	Cleveland	1979-1989	224	PEG	Retrospective	Gastro-colic fistula 2% Tube migration 2% Peritonitis 1% Intestinal obstruction 0.5% Total 6%*	0.9%
Beasley et al. (1995)	Melbourne	1989-1993	79	PEG	Prospective	Tube migration 6% Oesophageal tear 1% Gastro-colic fistula 1% Total 8%*	0%
Khattak et al. (1998)	London	1990-1995	130	PEG	Retrospective	Peritonitis 6% Gastro-colic fistula 3% Intestinal obstruction 3% Major Haemorrhage 3% Total 15%*	0.8%
Segal et al. (2001)	Lille	1990-1997	110	PEG	Retrospective	Buried Bumper 15% Major infection 3% Peritonitis 2% Gastro-colic fistula 1% Total 21%	0%

Vervloessem et al. (2009)	Rotterdam	1992-2008	467	PEG	Retrospective	Major infection/granulation 3% Buried Bumper 2% Peritonitis 1.5% Gastro-colic fistula 1% Major Haemorrhage 0.6% Tube migration 0.4% Oesophageal perforation 0.2% Total 9%*	0.2%
Sathesh-Kumar et al. (2009)	Luton	1995-2007	161¶	PEG	Prospective	Buried Bumper 12% Major infection 8% Tube migration 5% Gastro-colic fistula 3% Intestinal obstruction 1% Total 29%*	0%
McSweeney et al. (2013)	Boston	1999-2000	138	PEG	Retrospective	Major infection 7% Tube migration 1% Granulation 1% Intra-operative malpositioning 1% Buried Bumper 1% Total 11%	0%

*- Rate adjusted according to my definition

Table 1-1 Literature review of complications following PEG insertion

¶Includes new PEG & change of PEG to PEG

1.5.2 Jejunostomy

There is very little data on the long-term follow up and complications after jejunostomy, in adults or children. The available studies in the paediatric population are summarized in Table 1-2. As with gastrostomy studies, the definition of ‘major’ complications is not uniform and therefore not comparable. Gastro-jejunal tubes have been reported to be inconvenient as long term feeding tubes due to the need of device re-insertion after frequent dislodgement (Godbole et al., 2002).

Author (year of publication)	Place	Study date	n (age)	Type of Jejunostomy	Study type	Major Complications	Death
Smith and Soucy (1996)	Ottawa	1982-1994	64 (57 children 7days-23 years old)	Surgical (Witzel Tube)	Retrospective	Dislodgement 9.4% Infection 9.4% Intraperitoneal 6.2% Intestinal obstruction 1.6% Jejuno-jejunal fistula 1.6% Ileal placement 1.6% Wound dehiscence 1.6% Total 31.4%*	5%
Williams et al. (2007)	Leeds	1998-2003	35 (0.1-16 years)	Surgical (Roux en Y)	Retrospective	Peristomal leak 17.1% Dislodgement 8.6% Peristomal infection 5.7% Jejuno-colc fistula 2.9% Abdominal wall abscess 2.9% Total 37.2%	0%
Egnell et al. (2014)	Karolinska	1996-2010	33 (0.15-17.7 years)	Surgical (Witzel Tube)	Retrospective	Dislodgement 6% Intestinal obstruction 9% With perforation 3% With perforation & wound dehiscence 3% Peristomal leak 6% Wound dehiscence 6% Total 33%	0%

Table 1-2 Literature review of complications following jejunostomy insertion

*- Rate adjusted according to my definition

1.6 Scientific analysis of complications

1.6.1 Background

Historically, mortality has been the measure to assess the risk of surgical procedures (Clavien et al., 1992). However, with the improvement in post-operative care and better survival, factors such as morbidity, quality of life and cost have become more important. In 80% of the reported studies describing complications there is no mention of the severity (Martin et al., 2002). The reporting of complications is inconsistent and incomplete. There is lack of standardization of complications and consequent under-reporting. A 'minor' complication by one might be classed as 'moderate' complication by another. This also leads to difficulties in surgical comparative trials and other studies, where incidence of complications is compared between procedures, where it might be concluded that a procedure with frequent minor complications is inferior to a procedure with infrequent, but life-threatening, complications.

1.6.2 Categorization of Adverse Events

In 1992 an attempt to differentiate 'complications' from 'failure to cure' and 'sequelae' was made (Clavien et al., 1992). Complications were classed according to the degree of invasiveness of the treatment needed to correct the complication.

1.6.3 Clavien-Dindo classification

In 2004, Clavien and Dindo modified the classification, leading to the Clavien-Dindo classification. It describes five grades of severity for most known complications (Table 1-3) (Dindo et al., 2004). Usually the single most severe complication is reported, while 'ignoring' others. It therefore does not represent the overall morbidity of a procedure. However, it is simple, very easy to replicate and can be used in different parts of the world consistently.

This classification has been used extensively in numerous studies across various surgical fields, especially in adults.

TABLE 1. Classification of Surgical Complications

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
	Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications
	Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

Table 1-3 Clavien-Dindo classification for surgical complications (Dindo et al., 2004)

1.6.4 Comprehensive Complication Index (CCI)

To report the overall morbidity after a surgical procedure, the CCI was developed (Slankamenac et al., 2013). The authors conducted a series of studies to develop and validate a unique comprehensive scoring system, based on the well-established Clavien-Dindo classification. It includes all negative events that occur after a procedure, with their respective severity. CCI weights severe complications more heavily than multiple complications of lesser severity. Low-grade complication contributes less and less in combination with more severe complications in the overall post-operative assessment. It is reproducible for analysis and can detect clinically relevant signs. It promises to be a readily assessable (www.assessurgery.com) and easily reproducible method of quantifying the overall burden of postoperative complications.

The CCI has been developed and validated on a wide spectrum of adult patients undergoing a variety of major and minor general surgical procedures. However, it has not been validated on paediatric patients and may not be pertinent to the complex paediatric patient. It should only be used with caution to evaluate complications in paediatric surgical patients.

Aims & Objectives

My overall aims in this thesis are to investigate different enteral feeding methods and their complications in children.

The specific objectives were:

(i) **to determine the better method of gastrostomy insertion**, with the hypothesis that percutaneous endoscopic gastrostomy (PEG) is superior to radiologically inserted gastrostomy (RIG) – by undertaking a randomised controlled trial

(ii) **to investigate a major complication of percutaneous gastrostomy - specifically buried bumpers** – by reviewing the incidence, associated risk factors, treatment and prevention strategies

(iii) **to investigate jejunal feeding methods** – specifically surgical jejunostomy feeding and radiologically inserted gastro jejunal feeding in terms of risks and benefits and nutritional outcomes

(iv) **to compare scoring systems to quantify patient outcome** in a prospectively collected patient sample – specifically Clavien Dindo scoring, Comprehensive Complication Index and PEG vs. RIG scoring system

(v) **to develop a novel tool to measure morbidity in the paediatric surgical patient** – a preliminary study to develop a Paediatric Complexity Index (PCI) for risk stratification of paediaric surgical complications.

Chapter 2 Randomised controlled trial of gastrostomy techniques: The PEG vs. RIG Trial

2.1 Background

Percutaneous endoscopic gastrostomy (PEG) is a widely used and well accepted method for gastrostomy insertion in children (Gauderer et al., 1980) Radiologically-inserted gastrostomy (RIG) has similarly become widely accepted (Tao and Gillies, 1983). Although both techniques require a general anaesthetic, RIG has a potential advantage from a service provision point of view in that an operating theatre slot is not required, so that waiting times for gastrostomy may be shorter. A retrospective review conducted by Nah et al. (2010) of 331 children who had a gastrostomy inserted between May 2004 and July 2008, showed that the overall complication was lower in PEG as compared to RIG (28% vs. 47%, P=0.001) (Figure 2-1). They also concluded that oncologic patients, the younger child and those with higher weight z-scores were more likely to have complications. However, the study being retrospective has the inherent disadvantage of the two study populations being unmatched. The PEG group of patients were mostly neurologically impaired, while the RIG group of patients had mostly oncological or gastrointestinal disease. The latter group are more likely to be immuno-compromised and on chemotherapeutic agents, making them prone to complications such as delayed healing and infections (Barron et al., 2000). The other significant problem was the different referral pathway for PEGs and

Table 3 Complication rates and scores

	PEG (n = 125)	IG (n = 193)	*P*
Patients with any complication	35 (28%)	90 (47%)	.001
Patients with major complication	1 (1%)	6 (3%)	NS
Complication score/month of follow-up	0 (0, 0.9)	0 (0, 9.1)	.03

Patients with any complication refers to the number of patients who had any complication from gastrostomy insertion to follow-up. Major complication refers to the number of patients who had any complication requiring surgical intervention from gastrostomy insertion to follow-up. Number of patients with complications in the PEG and IG groups were compared using Fisher's Exact test. Complication score/month of follow-up is the complication score defined as in Table 1 divided by follow-up time in months. Data, expressed as median (range), were compared using Mann-Whitney test.

Figure 2-1 Complications after PEG and RIG from Nah et al. (2010)

RIGs at the hospital. The authors attempted to take account for these differences by using zero-inflated Poisson regression analysis but concluded that *'RIG patients still had a higher complication rate than did PEG patients. Nevertheless, such conclusions should ideally be confirmed by a randomized controlled trial'.*

2.2 Hypothesis

The hypothesis to be tested is that percutaneous endoscopic gastrostomy (PEG) is superior to radiologically inserted gastrostomy (RIG) in terms of outcome and complications.

2.3 Aim of the study

The aim of this trial was to investigate this hypothesis by conducting a randomised controlled trial. Both PEG and RIG have the benefits of easy insertion and avoidance of a laparotomy incision. However, both techniques are also associated with complications, including gastro-colic fistula, haemorrhage, buried bumper and intra-abdominal leak with sepsis (Wollman et al., 1995, Cosentini et al., 1998, Vervloessem et al., 2009, Campos and Marchesini, 1999, Singh et al., 2013). Although there are a number of publications on both methods in the adult population (Wollman et al., 1995, Cosentini et al., 1998, Barkmeier et al., 1998, Leeds et al., 2010, Blondet et al., 2010), there is little information available in the literature specifically comparing the two techniques in the paediatric population. A recent Cochrane review highlighted the lack of evidence in this area, as no randomised controlled trials comparing PEG with RIG were identified, either in adults or in children (Yuan et al., 2016).

2.4 Methods

2.4.1 Participants

The PEG vs. RIG trial was a double-blinded single centre randomised controlled trial. Two hundred and fourteen patients (n = 107 in each arm) were randomised to either PEG or RIG. I co-ordinated the trial, consented and randomised patients. As I also co-ordinated the booking of PEG or RIG onto the relevant operating list, it was not feasible for me to be blinded. The patient and parents or guardian were blinded to the method of gastrostomy insertion used. To ensure the blinding of the patients and assessors, I used a standard information sheet and consent form. The operation note was placed in a sealed envelope in the clinical notes. The post-operative gastrostomy wound for either PEG or RIG was dressed similarly. All patients and their caregivers were counseled after the procedure by the same specialist gastrostomy nurses who were not part of the trial, at which they were given standardized post-gastrostomy care advice and an information pack. Routine clinical follow up was performed as per normal practice.

The research nurses assessing the outcomes (complications) were also blinded. For the assessment at follow-up of the patients, I organised training of the research nurses at the Somers Clinical Research Facility in Great Ormond Street Hospital. These nurses had no access to the patients' clinical notes. I also designed a standard follow-up questionnaire to aid this (Appendix 3).

The recruitment started in November 2011 and finished in November 2014.

2.4.2 Inclusion Criteria

The inclusion criterion was defined as:

1. any child referred for gastrostomy insertion (including those with medically treated gastro-oesophageal reflux).

These patients were under the care of various clinical teams including: General Surgery, Oncology, Haematology, Endocrine, Metabolic, Gastroenterology and Nephrology.

2.4.3 Exclusion Criteria

Patients were excluded from the trial if they:

1. had gastro-oesophageal reflux and were being considered for anti-reflux surgery including fundoplication
2. had previous gastrostomy or fundoplication
3. had previous extensive abdominal surgery or
4. required a concomitant major procedure on the gut or other intra-abdominal organs.

There were no specific age or weight inclusion/exclusion criteria, but in order to be eligible, both the interventional radiology and surgical teams had to be potentially willing to perform the procedure.

2.4.4 Ethical Approval

The trial had ethical approval from the National Research Ethics Service (NRES) of the Health Research Authority. The registration number is: 10/H0713/47

The trial was registered with the ClinicalTrials.gov. ClinicalTrials.gov is a Web-based resource that provides patients, their family members, health care professionals, researchers and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions. The National Library of Medicine (NLM) at the National Institutes of Health (NIH) maintains the Web site. ClinicalTrials.gov Identifier: NCT01920438 2013.

The research was conducted in accordance with the Declaration of Helsinki (2001).

2.4.5 Randomisation

Patients were allocated to groups (1:1 allocation ratio) by weighted minimisation (Treasure and MacRae, 1998, Wade et al., 2006).

Minimisation is a method of randomised treatment allocation, which ensures that the groups are balanced with respect to prognostic indicators (minimisation criteria) that are likely to affect patient outcome. This is based on the idea that the next patient to enter the trial is given whichever treatment would minimise the overall imbalance between the groups at that stage of the trial. The patients were randomised online using a fast and simple method (SiMin® Window-based software, developed by the Institute of Child Health, UCL) to either PEG or RIG. The software was installed on a single password-protected computer, which was accessible only by me.

Minimisation criteria used are detailed in Table 2-1. The criteria were based on the conclusions of Nah et al. (2010) of children with certain diagnosis, younger age and greater weight being prone to complications. To avoid the operational confounders of pathway of patient referral the inpatient status is

Minimisation Criteria	Definition
Diagnosis	[Neurological] [Haematology/Oncology] [Metabolic] [Gastrointestinal Diseases] [Miscellaneous]
Age	[< 6months] [6 months – 2 years] [2 – 5 years] [>5 years]
Weight Centile	[<3%] [3-10%] [10-25%] [25-50%] [>50%]
Inpatient Status	[Yes] [No]
Scoliosis	[Yes] [No]
Gastro-esophageal reflux	[No] [Yes- Not needing anti-reflux surgery]

Table 2-1 Minimisation criteria

one of the criteria as well. It is widely recognised that children with difficult anatomy such as in scoliosis and with pre-existent gastro - oesophageal reflux might have more complications. So the six minimisation criteria used would make the two treatment groups very comparable.

2.4.6 Treatments and Schedules

When an eligible patient was identified, I discussed the trial with the parents and obtained informed consent. Patients were then randomised to either PEG or RIG. Procedures were performed by consultant radiologists or paediatric surgeons or by trainees at specialist registrar level under direct supervision by a consultant on site. All consultants had extensive experience with either RIG (interventional radiology consultants) or PEG (general surgery consultants). All cases were done under general anaesthesia with prophylactic antibiotics (co-amoxiclav unless contraindicated) administered before the procedure. A 9 French silicone gastrostomy tube was used (Freka, Fresenius, Runcorn, UK) which is approved (CE Marked) and marketed in the UK and EU.

The two standardized procedures compared in the trial were:

a) Percutaneous Endoscopic Gastrostomy (PEG)

After insufflation of the stomach with an endoscope, indentation of the stomach and transillumination through the abdominal wall was confirmed under endoscopic vision. A small incision was made over the area of maximum transillumination and a catheter mounted on a needle passed through followed by a guidewire. The guidewire was grasped by the endoscope, pulled out through the mouth and attached to the gastrostomy tube which was then pulled antegrade and out through the abdomen. The tube was fixed with an external fastener and no sutures were placed.

b) Radiologically Inserted Gastrostomy (RIG)

Oral contrast was given the night before the procedure to line the colon on

the day of procedure; enemas were not used. The stomach was insufflated with air via the nasogastric tube. Glucagon was not routinely used, although whether it was to be used or not was not stipulated in the protocol, and one interventional radiologist used glucagon as standard practise, whereas the others only used glucagon if it was difficult to delineate the stomach. RIG was performed using biplane fluoroscopy (Malden et al., 1992), with pre-placement ultrasonography for localization of the liver. An orogastric snare was passed and the stomach punctured under fluoroscopic guidance with an 18-gauge needle, which was used to insert a stiff 0.035-inch guidewire. This was snared and withdrawn through the mouth. The snare catheter was introduced in a retrograde direction from the abdominal wall to the mouth, and the gastrostomy tube was grasped and pulled down the oesophagus.

The stages of the trial were as follows:

Stage 1 – Enrolment

i) Patient was identified as eligible

ii) Informed consent was obtained from parents or guardian

iii) Demographics recorded and treatment randomised via randomisation software

Stage 2 – Day of Procedure

Details of operative procedure (technical failure, difficulty of procedure, operator details)

Stage 3 – Postoperative period

Data was collected until discharge of the patient from hospital.

Stage 4 – Postoperative Follow-up

Patients were re-evaluated at 6 weeks ± 2 weeks, 6 months± 1 month, 1 year ± 2 months and 3 years ± 2 months after the procedure. Complications were recorded and scored.

If by the time of evaluation, the participant had the gastrostomy removed, and there was no clinical indication for follow-up, the evaluation was stopped.

2.4.7 Outcome Measures

The primary end point of the study was the total number of complications (major and minor).

The secondary end points of the study were defined as:

i. major complication rate : colonic injury or gastro-colic fistula or other visceral injury, peritonitis requiring surgery, intestinal obstruction requiring surgery, major gastrointestinal bleed, other complications requiring surgery (including buried bumper)
ii. minor complication rate : infection requiring systemic antibiotics, delay more than 48 hours in establishing feeds, granulation, wound site discharge, tube-related problems (migration, dislodgement, leakage, breakage), other minor
iii. complication score : this is a score devised with weighting assigned to each complication depending on the severity of the complication, as detailed in Table 2-2. The score was devised in a consensus meeting attended by experts in the field (paediatric surgeons, interventional radiologists, junior doctors and specialist nurses).
iv. technical failure : these are the number of PEG or RIG that are unsuccessful and require conversion to open surgical gastrostomy or laparoscopic gastrostomy.
v. cost of hospital treatment
vi. mortality
vii. cause of death (relatedness to procedure / primary disease)

	Type of complication		Score
Major complications	Colonic injury / gastro-colic fistula		20
	Peritonitis requiring surgery		20
	Intestinal obstruction requiring surgery		20
	Major gastrointestinal bleed	Requiring surgery	20
		Requiring transfusion but not surgery	10
	Buried Bumper		20
	Other complications requiring surgery		20
Minor complications	Infection requiring systemic antibiotics		1
	Delay more than 48 hours in establishing feeds		1
	Granulation		1
	Wound site discharge		1
	Tube-related problems	Migration	1
		Pulled out / dislodged	5
		Leakage around tube	2
		Breakage	2
	Other minor		2

Table 2-2 Gastrostomy scoring system for complications of gastrostomy insertion

2.4.8 Sample Size

The sample size was based on the primary end point of complications and was determined using the best available evidence at the start of the trial. This was based on the previous retrospective review of 331 children who had either PEG or RIG (Nah et al., 2010). The review showed that 28% of PEG patients and 47% of RIG patients had complications (Figure 2-1).

For sample size estimation, we used a binary superiority power calculation, i.e. proportion of patients with any complications in each group.

To detect a difference of 19% (80% power, significance level =0.05), 100 patients per group were needed.

At Great Ormond Street Hospital, a large number of gastrostomies are performed per year (between 3-5 per week), and it was estimated that 200 patients would be recruited within 2 years.

2.4.9 Trial Management

There was some delay in starting the trial, to ensure agreement between the researchers, Somers Clinical Research Facility and Research & Development (R&D) Office. To set-up the randomized controlled trial I had discussions with the Interventional Radiology and General Surgery operational units. I also had discussions with the Somers Clinical Research Centre and the Research & Development (R&D) governance team. Ethical amendments were obtained to alter the original protocol in order to correct and clarify various details of the study, and also to include a follow-up window. These were approved by the ethics committee and by the R&D team. The recruitment began in November 2011 and finished in November 2014.

The trial involved recruitment of patients needing a gastrostomy. The patients were under the care of various clinical teams including: General Surgery, Oncology, Haematology, Endocrine, Metabolic, Gastroenterology, and Nephrology. I organised departmental meetings and discussion with the clinicians involved in the care of the patients. I had one-to-one discussions with the nephrologists, oncologists, gastroenterologists, haematologists and general surgeons about individual patients. I put up flyers in the outpatient clinics providing more information.

Initially, it was difficult to schedule patients for their procedure once recruited and allocated, but I had discussion and meetings with the operators involved and the process was streamlined. Since then the process ran effectively and there was no delay in patients receiving a gastrostomy.

I managed the trial on a day-to-day basis. I assessed each referral for a gastrostomy against the inclusion and exclusion criteria. If the exclusion criteria were absent, I contacted the parents or caregiver of the referred child. I gave detailed information about the trial and addressed any concerns. If the child was judged to be of suitable age and maturity, I made every attempt to provide as much information as appropriate to the child regarding participation. I obtained informed consent for inclusion in the trial and consequently for randomisation. I randomised the patient online using SiMin® software to either PEG or RIG. Once randomised, I secured operating space for either PEG or RIG. I made sure that the interventional radiologist or general surgeon who performed the gastrostomy, were aware that the patient was in the trial and the group allocation is not disclosed. As I was co-ordinating the placement of PEG or RIG and their subsequent follow up by research nurses, I could not remain blinded.

I recruited and collected data for the patients at Great Ormond Street Hospital. I maintained the database and sorted out any problems identified by the nurses at follow-up. I wrote regular newsletters as the trial progressed to

keep the involved clinical teams up-to-date and also to introduce the trial to new doctors rotating through the General Surgery and Interventional Radiology units. I wrote reports for the trial funding body and ethics committee. The trial was overseen by the trial steering committee and monitored by an independent data monitoring and ethics committee.

2.4.10 Statistical Methods

Data were entered into Microsoft Excel 2010 analysed using SPSS (Version 22) and Stata InterCooled version 12.

Data were analysed by Poisson (number of complications) or zero-inflated Poisson (complication score), with all the minimization criteria as covariates. Follow-up times were compared by a Mann-Whitney test.

2.4.11 Data Monitoring and Interim Analysis

Participants were allocated a unique study number, and all study data were stored with this number as the identifier. Identifiers were held in a separate database. Data was analysed at the Institute of Child Health.
It was recommended to convene a Data Monitoring and Ethics Committee (DMEC), which would review the data when 100 patients had been recruited. The DMEC would be independent of both the trial organisers and those providing therapy. This committee would perform interim analyses to:
a) review assumptions underlying sample size considerations;
b) modify or close intake to trial.
The criteria for stopping the trial were defined as:

(i) a significant difference ($p<0.01$) between the two arms in overall complication rate; or
(ii) significantly ($p<0.01$) greater incidence of major complications; in one arm compared to the other, analysed both as single outcomes and as total cumulative complications.

The Data Monitoring and Ethics Committee was convened on 25th September 2013 (DMEC Report – Appendix 4). By this time 125 patients had been recruited into the trial, but for the purpose of interim analysis 100 patients were reviewed (as defined in the trial protocol, Appendix 1). The DMEC did not have any ethical concern and recommended to continue intake into the trial to complete the originally set out target of 200 patients.

2.5 Results

2.5.1 Participant flow

The flowchart in **Figure 2-2** demonstrates the flow of participants through each stage of the trial (assessment, enrolment and treatment) according to the CONSORT guidelines (Moher et al., 2010) for reporting. Three hundred and thirty-nine patients were assessed for eligibility and 214 were enrolled in the trial. One hundred and twenty-five patients were excluded from the trial (Table 2-3). Fifty-six patients were not eligible due to various reasons – 31 did not meet the inclusion criteria, 11 did not need a gastrostomy any more, 6 terminally ill patient required the gastrostomy as a part of palliative treatment, 6 patients had complex neuro-muscular disorder and were following individualised treatment pathway which included PEG placement and 2 patients had anaesthetic risk too great for procedure to be performed in the interventional radiology suite. Sixty-nine patients were eligible but not enrolled. Thirty patients declined to participate in the trial, 19 patients needed urgent gastrostomy and both PEG and RIG slot were not available so could not enter the trial, 18 patients were foreign resident, so unlikely to be able to complete the follow-up, 2 patients were under the child safeguarding team without designated parental responsibility.

Not meeting inclusion criteria	31
No longer needed	11
Palliative	6
Complex patient, following Neuro-muscular pathway	6
Complex anaesthetic issue, not suitable for IR suite	2
Eligible but not enrolled	
Declined	30
Urgent, no similar slot for PEG/RIG	19
Foreign resident/no fixed abode	18
Safeguarding issue, child in transitional care	2
Total Eligible but not enrolled	69
Total excluded after assessment	125

Table 2-3 Characteristics of patients excluded after assessment

Of the 214 randomized patients, 107 were allocated to each arm (PEG and RIG). Two patients randomized to RIG received a PEG. One patient, who had been randomised to RIG, had Treacher Collins Syndrome. At pre-anaesthetic work-up it was realized that on previous anaesthetic for a microlaryngoscopy and bronchoscopy the patient had a difficult airway and had needed two senior anaesthetists. It was decided that for a patient with such an airway, it would be in his best interest to operate in the operating theatre suite which is better equipped for complex patients rather than the interventional radiology suite. He was therefore, re-scheduled to have a PEG after being randomized to RIG. Another patient, who had been randomised to RIG, had a PEG; as on the day of the operation a major incident in the interventional radiology suite meant that he was cancelled. However, a cancellation on the general surgery operating list resulted in him having a PEG on the same day. Available demographics and follow up for these patients are included in RIG dataset analysis on an intention to treat basis. Sixteen further patients did not receive their intervention, and five patients had no follow-up, as indicated in Figure 2-2, so that 97 patients were analysed for the primary outcome in the PEG group and 96 in the RIG group.

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram

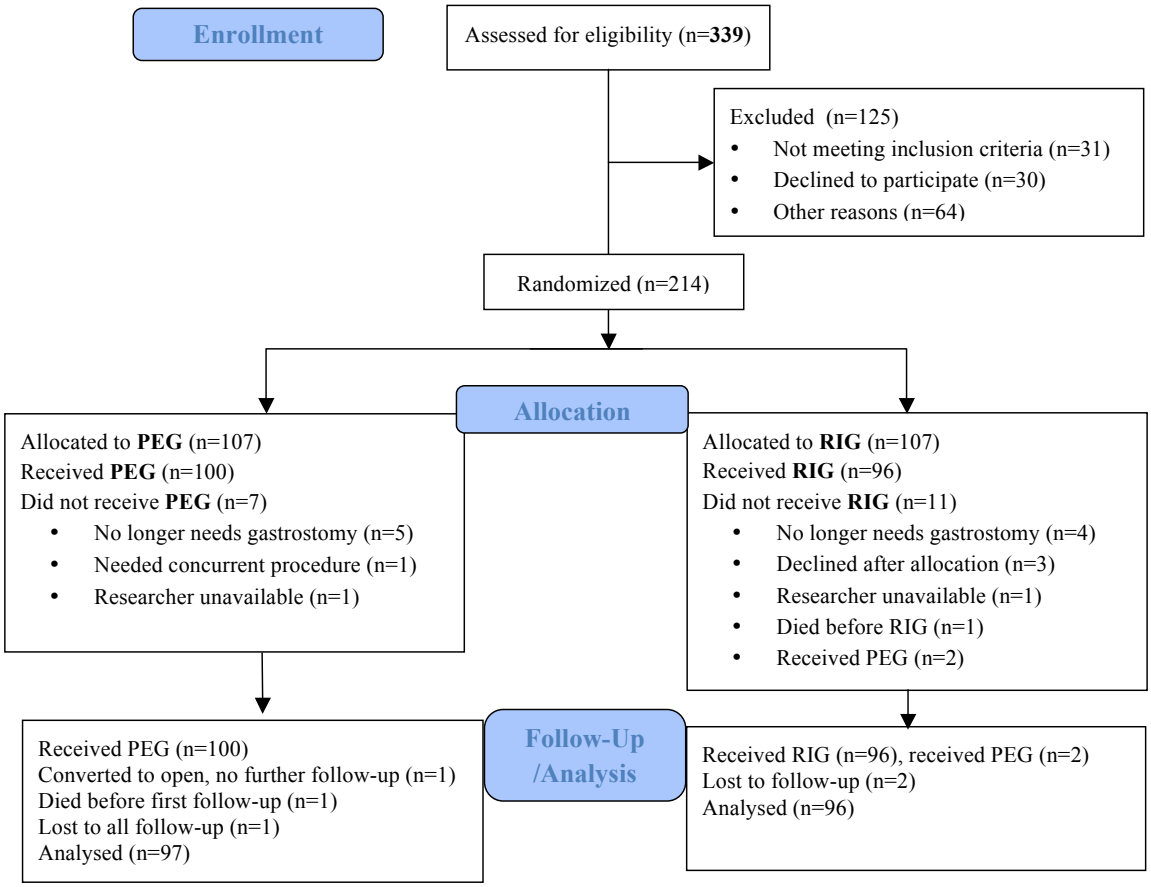


Figure 2-2 CONSORT diagram indicating patient flow through the trial

2.5.2 Recruitment

Patients were recruited between November 2011 and November 2014 (Figure 2-3). They were followed up at 6 weeks, 6 months, 1 year and 3 years after procedure.

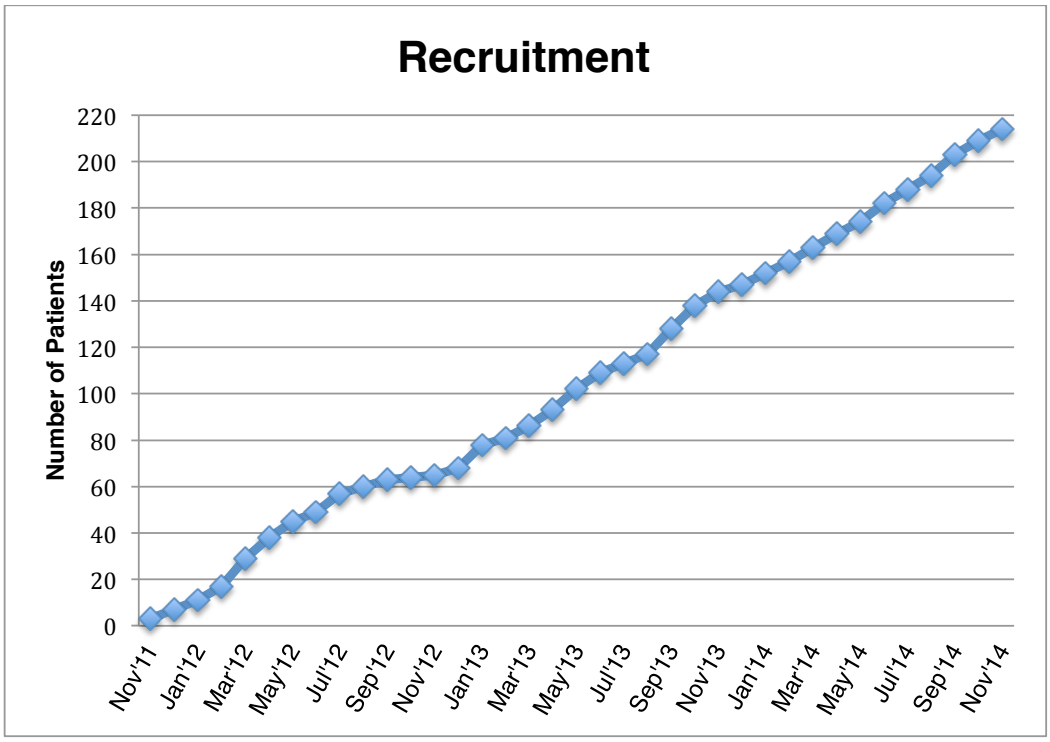


Figure 2-3 Chronological progress of patient recruitment

An independent data monitoring and ethics committee (DMEC) was convened and reviewed data on the first 100 patients recruited. The committee did not have any ethical concern and recommended to continue the intake into the trial to complete the target of 200 patients. After 36 months 214 patients were recruited and 198 (100 PEG and 98 RIG) received their intervention.

2.5.3 Baseline data

The 214 children enrolled were randomised to either PEG or RIG with minimisation using the SiMin® software. There were 100 PEG and 98 RIG for analysis. Patients in the two groups were well matched, with no significant differences in any of the demographic or clinical variables measured (Table 2-4). For the purpose of analysis, the two patients who had been initially

Criteria	PEG	RIG	p*
Diagnostic Group			
Neurological	32	29	0.76
Haematology/Oncology	24	24	1
Metabolic	12	13	0.83
Gastrointestinal disease	1	2	0.62
Miscellaneous	31	30	1
Age			
<6months	6	5	1
6months-2years	35	36	0.88
2-5years	26	32	0.35
>5years	33	25	0.28
Weight centile			
<3%	35	34	1
3-10%	18	16	0.85
10-25%	11	12	0.83
25-50%	15	15	1
>50%	21	21	1
Inpatient status			
Inpatient	9	9	
Outpatient	91	89	1.00
Scoliosis			
Yes	3	0	
No	97	98	0.25
Gastro-oesophageal reflux			
Yes-Not needing anti-reflux surgery	24	27	
No	76	71	0.63
Group Totals	100	98	

Table 2-4 Patient demographics and clinical characteristics

*Chi^2 test for independence

allocated to RIG, but had PEG due to anaesthetic and practical issues have been analysed as RIG on an intention to treat basis. There were only 1 PEG and 2 RIG patients with primary gastrointestinal disorder, as most of the children requiring a gastrostomy with a gastrointestinal disease were operated in the gastro suite.

2.6 Primary Outcome Measure – Number of complications (major and minor)

Follow-up was for median of 1 year (range 6 weeks to 3 years) in each group, and was similar between the groups (p=0.474). The number of patients in each group attending each follow-up is shown in Table 2-5. The total number of complications after PEG and RIG were as in Table 2-6.

	PEG (n=97)	RIG (n=96)
6 weeks	91	94
6 months	86	80
1 year	69	68
3 years	32	36

Table 2-5 Number of patients attending each follow-up

(In addition to patients failing to attend follow-up, and mortalities, other reasons for non-follow up were gastrostomy removal or conversion to a balloon secured device).

	PEG (n=97)	RIG (n=96)	Total
Major Complications	2	3	5
Minor Complications	79	78	157

Table 2-6 Number of patients with complications after PEG/ RIG

Only five patients experienced a major complication, two in the PEG group (2%) and 3 in the RIG group (3%). The distribution of number of complications in each patients group is shown in Figure 2-4.

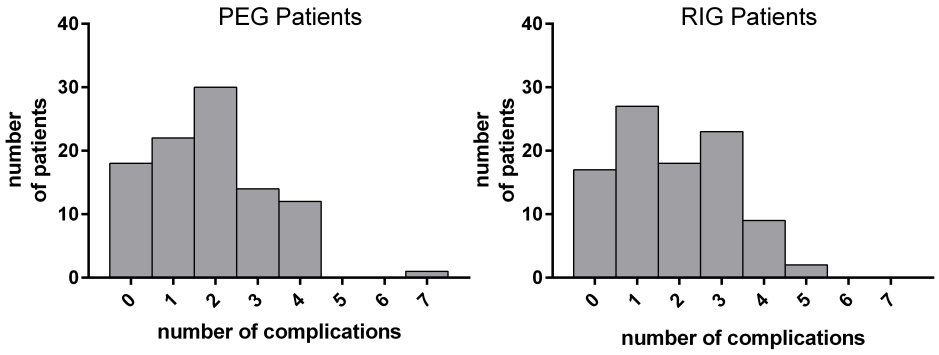


Figure 2-4 Distribution of complications between PEG and RIG

Factor	Incidence rate ratio (95% CI)	p-value
RIG	0.98 (0.80 - 1.21)	0.875
Age (per year increase)	0.99 (0.96 - 1.03)	0.700
Haematological/Oncological	0.97 (0.70 - 1.34)	0.846
Metabolic	1.19 (0.85 - 1.66)	0.303
Gastrointestinal	1.06 (0.56 – 2.00)	0.864
Miscellaneous	0.92 (0.70 - 1.20)	0.536
Weight centile	1.00 (1.00 - 1.00)	0.601
Inpatient	1.23 (0.79 – 1.91)	0.357
Scoliosis	0.70 (0.17 – 2.85)	0.615
Gastro-oesophageal reflux	1.24 (0.96 - 1.60)	0.105

Table 2-7 Poisson regression analysis of total number of complications (major and minor)

Adjusted for length of follow-up, and the minimization criteria. Incidence rate ratios are compared with a neurologically impaired four-year-old outpatient on the 25th centile for weight, without reflux or scoliosis, having a PEG, in whom the total number of complications is 1.23 (95% CI 0.97 – 1.56).

The number of complications per patient was analysed by standard Poisson regression, as this allows adjustment for different lengths of follow-up (Table 2-7). A standard Poisson analysis was used rather than zero-inflated as the Vuong test indicated that zero-inflated Poisson was not a better fit to the data (p=0.5). A neurologic 4-year-old outpatient on the 25th centile for weight having a PEG, with neither reflux nor scoliosis was used as the reference patient to compare other variables. Compared with this reference patient, RIG patients had a similar rate of complications to PEG patients (0.98 [95% CI 0.80-1.21]-fold lower rate of complications, p=0.875). None of the minimization criteria showed a statistically or clinically significant effect on rate of complications.

2.7 Secondary Outcomes

2.7.1 Major complication rate

There were two patients with major complications in the PEG group. A neurologically impaired one-year old patient developed a buried bumper. It was discovered during routine replacement of the device being attempted in the Interventional Radiology suite, 2 years following insertion. The parents did have problems with leaking around the gastrostomy site for some time and had the end of the Freka tube replaced a few times before. She had the buried bumper removed endoscopically and replaced by another PEG. Another 5-year-old oncology patient had the gastrostomy tube passing through the liver, which was discovered incidentally on a CT scan after 3 years. He is due for surgery to have this removed.

There were three major complications after RIG, each requiring a general anaesthetic. A two years old girl with neurological impairment and feeding problems secondary to hypoxic ischaemic encephalopathy had a RIG inserted. She developed abdominal pain and discomfort post operatively. She was managed conservatively initially, however, 11 days later she needed a laparotomy. She had a gastro-colic fistula, which was closed and a new gastrostomy was fashioned. A two years old boy with epilepsy and learning disorder developed an abscess at the gastrostomy site in the immediate post-operative period. It was aspirated under a general anaesthetic. A five-year-old child with hyperinsulinism developed feeding difficulty with the gastrostomy and was discovered to have a buried bumper during tube replacement and needed a laparotomy and excision of inflammatory mass three years after the initial procedure.

2.7.2 Minor complication rate

The minor complications for the patients were as in Table 2-8. The minor complications included wound infection, discharge, granulation, tube-related

problems (such as migration, dislodgement, leakage, breakage) and delay of more than 48 hours in establishing feeds caused by abdominal pain/temperature/nausea. One hundred and eight children (56 PEG and 52 RIG) had more than one minor complication. There was no significant difference between the two groups (p=1.00).

	PEG (n=97)	**RIG (n=96)**
Number of patients with minor complications	79	78
Number of minor complications	177	175
p-value*	1.00	

Table 2-8 Minor Complications

*Fisher's exact test comparing proportion of patients having any minor complication

2.7.3 Complication Score

The distribution of complication scores in the two groups and the complication score per year of follow-up is shown by diagnostic group in Figure 2-5 (a and b).

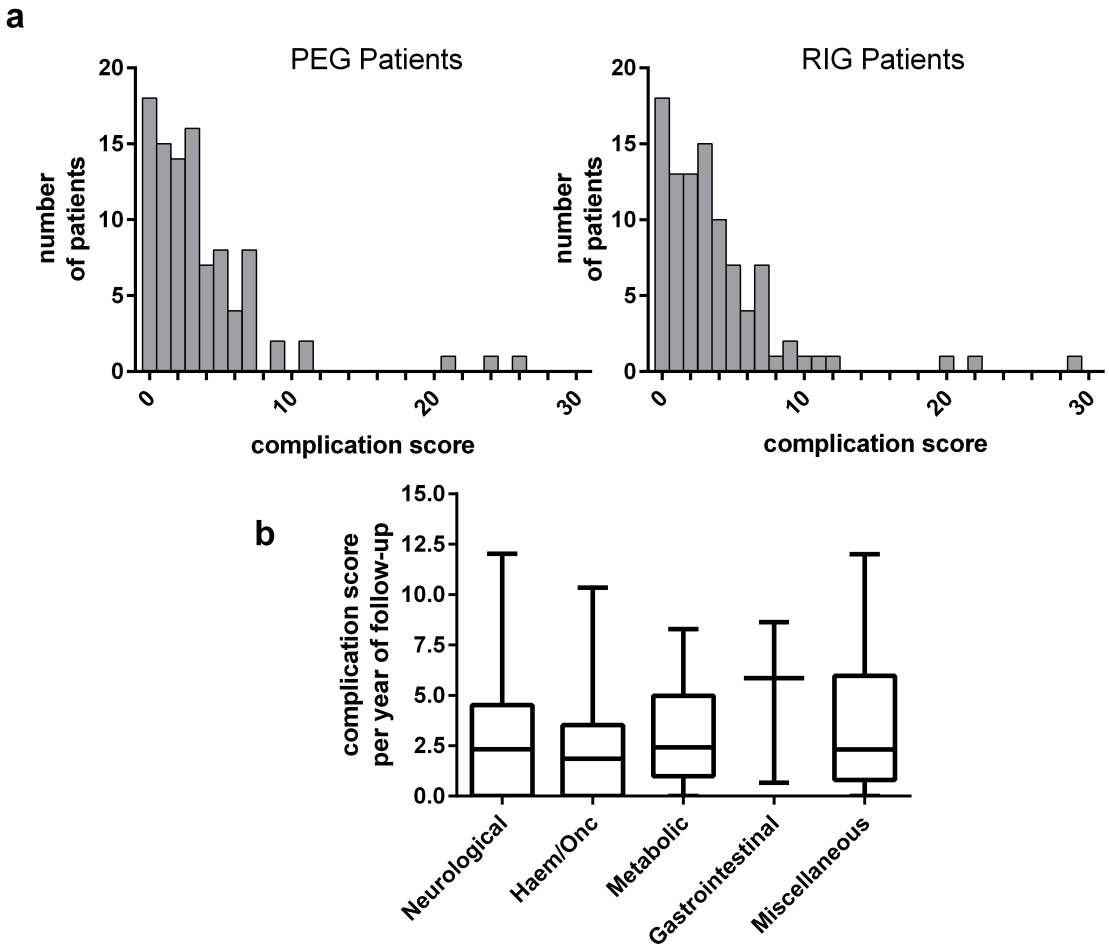


Figure 2-5 (a) Distribution of complication scores between PEG and RIG patients (b) Complication score per year of follow-up by diagnostic group.

Three outliers are excluded from figure b: a score of 520/year in the miscellaneous group (gastro-colic fistula 10 days after procedure), 35/year in the haematology/oncology group, and 25/year in the neurology group.

Although there were fewer patients (40/193) with a zero complication score, a Vuong test (which compares zero-inflated with a standard Poisson model) suggested that the zero-inflated model provides a better fit to the data (p=0.04). A neurologic 4-year-old outpatient on the 25th centile for weight having a PEG, with neither reflux nor scoliosis was used as the reference

patient to compare other variables. Compared with the reference patient, there was no statistically significant effect of having a RIG (1.04-fold higher complication score, p=0.597; Table 2-9). Although older patients had a statistically significant lower complication score (p=0.037), the magnitude of the effect (0.97 fold per year) was not great.

Factor	Incidence rate ratios (95% CI)	p-value
RIG	1.04 (0.89 - 1.21)	0.597
Age (per year increase)	0.97 (0.95 – 1.00)	0.037
Haematological/Oncological	0.88 (0.69 – 1.13)	0.321
Metabolic	0.86 (0.67 – 1.11)	0.254
Gastrointestinal	1.45 (0.99 – 2.12)	0.055
Miscellaneous	1.07 (0.88 - 1.31)	0.471
Weight centile	1.00 (1.00 - 1.00)	0.566
Inpatient	0.91 (0.63 - 1.32)	0.616
Scoliosis	0.62 (0.19 – 1.99)	0.420
Gastro-oesophageal reflux	1.05 (0.87 - 1.26)	0.597

Table 2-9 Zero-inflated Poisson regression analysis of complication score.

Adjusted for length of follow-up and the minimization criteria. Incidence rate ratios are compared with a neurologically impaired four year old outpatient on the 25th centile for weight, without reflux or scoliosis, having a PEG, in whom there is a complication score of 2.96 (95% CI 2.49 – 3.52), p<0.0005

2.7.4 Technical failure

There were two RIG failures. The first was a child with spastic quadriparesis and epilepsy, being fed through a naso-gastric tube, who also had scoliosis. An attempt to insert a RIG failed. The operating radiologist could not safely position a gastrostomy into the stomach due to the altered anatomy as a result of previously unrecognised scoliosis. She later had a successful PEG placement.

Another child with epilepsy and global developmental delay, who was fed via a naso-gastric tube, could not have a RIG. The operating radiologist could not find a safe window for placement of the gastrostomy. He later had a successful PEG placement.

There was one PEG failure. She was a child with Neuronal Ceroid lipofuscinosis (neurodevelopmental regression), infantile seizures and unsafe swallow. On attempted PEG placement, there was no recognisable light from the endoscope and the indent visible on endoscopy was immediately below the xiphisternum, which is not suitable for gastrostomy placement. The procedure was converted to open gastrostomy placement under the same anaesthetic.

2.7.5 Cost of hospital treatment

Although cost of hospital treatment was an outcome measure defined in the protocol, the hospital costing department were unable to provide reliable cost data on a per patient basis, so these data are not reported.

2.7.6 Mortality

Twenty-six patients died after a PEG/RIG insertion, all due to progression of their primary disease and none related to gastrostomy insertion or management. There was no significant difference between the two groups

(Table 2-10). One patient died within one month of gastrostomy insertion. It was reported as a Serious Adverse Event to the research and ethics committee (Appendix 5). The death resulted from severe and uncontrolled epileptic encephalopathy in a hospice. The ethics committee reviewed the death and concluded that it was not related to the intervention.

	Survival	**Death**	**'p' value***
PEG	84	16	0.29
RIG	88	10	

Table 2-10 Number of deaths in each group

*Fisher's exact test

2.7.7 Cause of death

In a number of children a gastrostomy insertion is a form of palliation. There were 6 children that were excluded from the trial as they were having the gastrostomy for ease of feed or administration of medications towards the end of their life, and that their inclusion in the trial was not justified. However, other children with life-limiting disorders died during the trial period. Most children who died had a haematological/oncological or immunosuppressive disorder or a life limiting inherited/metabolic disorder (Table 2-11). The deaths occurred 1-44 (median 13) months after the PEG/RIG insertion.

Patient Number	Diagnosis - Cause of death	Months since PEG/RIG
4	Congenital CMV, hydrocephalous, chronic liver disease	44
9	Propionic Acidaemia - Failed liver transplant	25
11	Medulloblastoma	7
22	Low grade glioma	2
25	Posterior fossa tumour	36
51	Cardiac rhabdomyosarcoma	13
54	Metastatic Medulloblastoma	13
67	ALL	6
77	Metastatic alveolar rhabdomyosarcoma	20
85	Menke's disease, seizures, progressive neuropathy	5
97	X linked chronic granulomatous disease	9
98	AML	4
102	Cartilage Hair Hypoplasia	9
105	Epilepsy - Cardio respiratory arrest due to recurrent pulmonary haemorrhages	28
108	Kearns-Sayre syndrome, hypomagnesemia hypocalcaemia, heart block, right sided ptosis & strabismus	24
115	Primordial dwarfism, bilateral hip dysplasia - Respiratory arrest	12
117	Glutaric Acidaemia Type 1	17
119	Cerebral Palsy	26
127	Infantile Pompe's disease	2
136	Cerebellar hypoplasia	13
138	Epileptic encephalopathy	1
140	Leukodystrophy, dystonia	15
141	AML - GvHD	22
153	Relapse ALL	19
161	Trisomy 21, Previous VSD, ASD, PDA repair	12
204	DOCK 8 deficiency	7

Table 2-11 Cause of death and the underlying disease

CMV = Cytomegalovirus, ALL = Acute Lymphoblastic Leukaemia, AML = Acute Myeloid Leukaemia, GvHD = Graft vs. Host Disease, VSD = Ventricular Septal Defect, ASD = Atrial Septal Defect, PDA = Patent Ductus Arteriosus, DOCK 8 = Dedicator of cytokinesis 8

2.8 Discussion

Although a previous retrospective review from the same hospital had suggested that there was a significantly higher rate of complications following RIG than PEG (Nah et al., 2010), this was not confirmed by this prospective randomised controlled trial, in which I showed that there is no difference in outcomes or complications between insertion of PEG or RIG. There was no pre procedure difference between the groups, and post procedure there were no significant differences between PEG and RIG in any of the secondary outcome measures. This difference between the retrospective review and the randomised controlled trial is probably due to significant demographic differences between the PEG and RIG populations in the retrospective review. In particular, in the previous study RIG group consisted of predominantly patients with a haematological or oncological primary diagnosis, whereas the PEG group consisted predominantly of patients with a neurological primary diagnosis.

The major complications observed during the trial, i.e. gastro-colic fistula, buried bumper and abscess requiring aspiration under a general anaesthetic are well recognised complications after a percutaneous gastrostomy placement (Schrag et al., 2007). A review of the literature (Table 2-12), suggests gastro-colic fistula to become apparent anywhere between 48 hours (Khattak et al., 1998) to 29 months (Gauderer, 1991) after insertion of a percutaneous gastrostomy. Our retrospective review over 13 years revealed buried bumpers in 20 children between 1 month to 5 years post percutaneous gastrostomy insertion (Singh et al., 2013) (Chapter 3). Given these durations of appearance of the complications it can be argued that the maximum follow up of 3 years in the trial is not long enough to capture all the complications. A gastro-colic fistula may become apparent only when the initial Freka device is being changed to a balloon secured device, as a change to another Freka does not lead to disruption of the tract, while the new Freka device is guided in. A buried bumper can remain asymptomatic

and undiscovered until the device is being replaced (Cyrany et al., 2016, Singh et al., 2013). However, although the development of a gastro-colic fistula is related to over-inflation of the stomach and small intestine, pulling the colon cranially and thus inter-positioning it in between the anterior abdominal wall and the stomach; the development of a buried bumper is on the other hand as a result of inadequate post insertion gastrostomy care. As the incidence of gastro-colic fistula might differ between the two insertion techniques, any difference in the rate of gastro-colic fistula between the two arms of the trial should be apparent within the 3-year follow-up. Conversely, as buried bumper is more dependent on adequate care rather than the insertion technique, the rate of buried bumper incidence should not be used as a benchmark to compare outcomes between PEG and RIG.

	Gastro-colic fistula timing post gastrostomy Median (range) in months	Buried bumper timing post gastrostomy Median (range) in months
Gauderer (1991)	5 (4-29)	
Beasley et al. (1995)	Post mortem finding	
Khattak et al. (1998)	10.5 (48hrs-18m)	
Segal et al. (2001)	8 (5-12)	18 (4-41)
Sathesh-Kumar et al. (2009)	17	24
McSweeney et al. (2013)		3
Singh et al. (2013)		30 (1-60)

Table 2-12 Literature review of gastro-colic fistula and buried bumper post percutaneous gastrostomy insertion

In this era of minimally invasive surgery, laparoscopic assisted gastrostomy insertion is becoming the preferred technique with some surgeons. The primary advantage being the ability to visualise the external wall of the stomach inside the abdomen, decreasing the chances of inadvertent injury to the transverse colon or other intra-abdominal viscus. Insertion of PEG or RIG is contraindicated in patients with upper airway obstruction such as in head and neck malignancy or severe burns and oesophageal obstruction. In such patients laparoscopic assisted gastrostomy insertion may be preferred over open gastrostomy insertion (Mizrahi et al., 2014). However, laparoscopic gastrostomy insertion may be associated with a significant increase in costs (longer theatre time, instrumentation cost etc.) and introduces a potential for additional difficulties that are not considerations for either PEG or RIG (e.g. anaesthetic considerations of laparoscopy). At the outset of the trial, we did consider whether to undertake a trial comparing laparoscopy with both PEG and RIG, but as laparoscopic gastrostomy was infrequently performed in our hospital, the decision was made to compare the two procedures which were most frequently performed, i.e. PEG and RIG.

In the trial we were successful in reaching the target number of patients, as per the power calculation. It was initially thought to be achievable in two years however; it took three years to reach the target. This was due to initial logistical problems. Subsequently, there was also significant delay due to lack of dedicated theatre time available for PEGs.

In the trial we believe we achieved successful blinding of the parents and the assessors, although this was not formally tested. Even though, some parents were curious to know their allocation, they understood the nature of the trial and did not insist on knowing the allocation. Although when the child enters radiology suite or operating theatre complex, it should be very apparent which arm of the trial the child is in; either due to parental anxiety or faith in the trial procedure, parents were not aware of the group allocation. I acknowledge that this was not a flawless process and during the study

design phase, there was consideration of performing the procedure in one suite. However the inconvenience of moving the dedicated fluoroscopic equipment, screens and endoscope to one site and then restricting the routine day-to-day usage where considered impractical. Parents who were unhappy to be blinded did not participate in the trial (30 out of 339 patients assessed for inclusion in the trial). The patient and parents or guardian were blinded to the method of gastrostomy insertion used. To ensure the blinding of the patients and assessors, I used a standard information sheet and consent form. The operation note was placed in a sealed envelope in the clinical notes. The post-operative gastrostomy wound for either PEG or RIG was dressed similarly.

The research nurses assessing the outcomes (complications) were also blinded. For the assessment at follow-up of the patients, I organised training of the research nurses at the Somers Clinical Research Facility in Great Ormond Street Hospital. The nurses had no access to the patients' clinical notes. I also designed a standard follow-up questionnaire to aid this (Appendix 3). The research nurses, who were assessing the outcomes, therefore were successfully blinded.

This cohort of patients with similar characteristics will enable us to do future follow up. The information achievable from this prospectively collated patient population will help answer questions related to the natural history of their disease and also the widely assumed notion that the insertion of a gastrostomy worsens gastro-oesophageal reflux (Thomson et al., 2011). Gastro-oesophageal reflux was not assessed objectively using pH-impedence study when the patients were enrolled into the trial. The inclusion into group with or without gastro-oesophageal reflux was made subjectively by the clinician assessing the child's symptoms and reflux management.

A preliminary analysis of the patients who had medically managed gastro oesophageal reflux at enrolment into the trial is as follows:

	No further procedure	Gastro-jejunal tube / anti-reflux surgery	Total	
PEG	18	7	25	
RIG	25	1	26	p = 0.02 *
Total	43	8	51	

Table 2-13 Follow up of patients with pre-existing gastro-oesophageal reflux

*Fisher's exact test

51 patients had documented gastro oesophageal reflux, i.e. 26% of all patients undergoing either PEG or RIG. Follow up of all these patients at a median of 3 years (2-4 years) after gastrostomy insertion showed that 8/51 (16%) of the patients with gastro oesophageal reflux had worsening of their symptoms necessitating either anti-reflux operation (n=3) or a gastro- jejunal feeding (n=5). There is a statistically significant difference in the requirement for further procedure between the PEG and RIG groups (Table 2-13). It is difficult to understand why a RIG patient might be less likely to have worsening reflux. One possibility is that the PEG patients would have had a routine clinical surgical follow-up and the surgeon might have had a bias towards an anti-reflux procedure, whereas the RIG patient routine clinical follow-up would have been by the paediatric speciality who might have had a higher threshold to referring to a surgeon for an anti-reflux procedure and would have been more likely to persist with medical therapy. This is very much a post-hoc analysis as requirement for anti-reflux procedure was not defined as an outcome measure in the protocol and the indications for performing an anti-reflux procedure were not defined. Nevertheless, this is an important issue for which longer-term follow-up is important to examine evolution of these patients with gastro-oesophageal reflux.

A formal cost analysis of the two procedures was unfortunately not undertaken as the hospital costings department were unable to provide data

suitable for a comparative analysis. In addition, such a comparison would be difficult because of the multiple co-morbidities present in many of the patients. However considering that both procedures would have a general anaesthetic and single night post-procedure hospital stay (for patients admitted for the procedure), the difference in cost would be down to the equipment used. In the case of PEG, this would be the cost of endoscopy and relative cost of time in the operating theatre versus interventional radiology suite and in the case of RIG, ultrasound, contrast medium and X-rays.

One weakness of the trial was difficulty in comparison of the complications in the two groups. Although we developed and used a complication scoring system specific for gastrostomy, a more generalisable scoring system specific for, and validated in, the paediatric population is much needed. Older patients had a significantly lower rate of complications, however the magnitude of the effect (0.97 fold per year) was not great. This was similar to our previous retrospective review (Nah et al., 2010) and has been shown in other studies (Goldberg et al., 2010). Our retrospective review (Nah et al., 2010) suggested a higher complication rate in patients with higher weight z scores, however we did not detect this difference. In the current prospective trial, we found no difference in the rate of complications in haematology/oncology patients as compared to neurological patients, which is contrary to our findings in the retrospective review (Nah et al., 2010). Haematology/oncology patients might be expected to have a higher rate of infective complications and complications related to wound healing, because of immunosuppressive drugs. However, these complications only achieve a low score, whereas complications requiring further procedures and/or anaesthetics are assigned a higher score. No patient in the haematology/oncology group had a major complication, whereas major complications were observed in the neurological, gastrointestinal and miscellaneous groups. Conversely, haematology/oncology patients are less likely to have disordered gastric function when compared with the neurologic

patients in whom limited stomach compliance affects tolerated feed volume and leakage back along the gastrostomy tract.

Technical failures occurred during the trial; there were two RIG failures necessitating a PEG, and one PEG failure necessitating an open gastrostomy. This is a potential disadvantage to the RIG, in that technical failure would require rebooking a theatre slot and a second general anaesthetic, whereas failure of a PEG can be converted to an open procedure under the same anaesthetic. RIG necessitates a radiation dose, with a dose-area product <0.1 μGy m^2 for patients <15 kg, and <0.2 μGy m^2 for patients 15-30 kg. Technical failure was considered as a separate outcome in the protocol, so we have not considered these as complications. It would therefore be accurate to describe the trial outcomes as post-operative complications to reflect this issue.

Although the trial was powered to detect the total number of patients experiencing complications, on the basis of our own retrospective review (Nah et al., 2010), we also acknowledge that the trial was under-powered to detect a significant difference in incidence of any individual complication, such as gastro-colic fistula. The trial was designed to compare the incidence of complications, however, there may be other factors influencing the decision of whether to perform a PEG or a RIG, e.g. availability of procedure slots/ surgeons/ radiologist, relative cost of procedure etc. The finding of no significant difference in complications between the procedures allows decisions to be made on these other factors without compromising results. There is a limited literature on RIG in children; a recent systematic review and meta-analysis of gastrostomy placement in children (Baker et al., 2015) identified only our own retrospective review (Nah et al., 2010). We believe that the findings from our study are applicable to other centres with a paediatric interventional radiology service. Although many patients in each group experienced complications, most of these are minor complications and we believe that the benefits of insertion of a secured gastrostomy for long-

term use outweigh the risks of repeated aspiration and/or accidental tube removal and replacement if a nasogastric tube were to be used for an extended period of time. As our retrospective review suggested a significantly higher rate of complications in the RIG group, we designed the study as a superiority trial. In order to determine equal effectiveness, it would have been necessary to perform a non-inferiority trial with a suitable definition of non-inferiority trial. Nevertheless, major complications were rare in both PEG and RIG and so we feel that both procedures are clinically safe. RIG gave a 0.98 (95% CI 0.80-1.21)-fold lower rate of complications, and a 1.04 (0.89-1.21)-fold higher complication score rate than PEG, so there is no evidence from this trial that PEG is superior to RIG.

2.9 Conclusions

In conclusion, in patients for whom a percutaneous gastrostomy is appropriate, there is no evidence that either PEG or RIG leads to a significantly higher number of complications or complication score, which is contrary to a previous retrospective review. This indicates the importance of, when possible, undertaking prospective studies or RCTs to verify the conclusions from retrospective series in which differences are found. Further follow-up of these patients will indicate whether the equal efficacies of these procedures are still apparent at a later date.

Chapter 3 Management of a complication of percutaneous gastrostomy in children: Buried Bumpers

3.1 Background

Buried bumper is a rare but major complication after insertion of a gastrostomy. The internal bumper or flange migrates along the gastrostomy tract out of the stomach. The flange can lie anywhere between the stomach mucosa and the surface of the skin (Figure 3-1)

This can be attributed to excessive tension between the external bolster and the internal bumper of the gastrostomy device causing pressure necrosis of the tissue in between (DeLegge et al., 2006). The gastrostomy tract evolves into an abscess cavity with infiltrate surrounding the migrating disc. The gastric mucosa covers the internal surface of the flange of the gastrostomy tube, therefore, giving rise to symptoms such as resistance upon infusing feeds, pain and peri-tubular leakage. The incidence has been reported to be 1.3 to 21.8% in the paediatric population (Sathesh-Kumar et al., 2009, Furlano et al., 2008, Kohler et al., 2008, Binnebosel et al., 2010, Hodges et al., 2001, Segal et al., 2001). I reviewed the incidence and management of

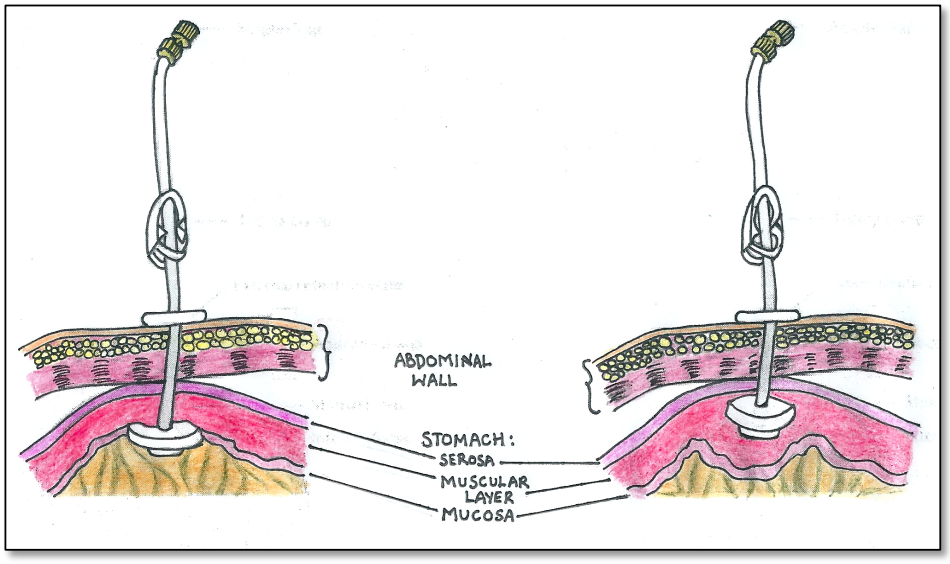


Figure 3-1(a) Correct position of a percutaneous gastrostomy (PEG) (b) Buried bumper

buried bumpers over 12 years.

3.2 Patients and methods

I obtained institutional ethical approval. I analysed the surgical and interventional radiology database from August 1999 to May 2011. I reviewed the records for children with buried bumper. I collected the demographic information, clinical diagnosis, symptoms at presentation, age at time of procedure, date of procedure, operative details, early and delayed complications, and length of follow-up. The percutaneous gastrostomy inserted in all cases was a 9 French silicone gastrostomy tube (Freka, Fresenius, Runcorn, UK). I conducted a telephonic interview with the parents of these children with focussed assessment of the care of the gastrostomy tube prior to the episode of buried bumper.

3.3 Results

Patient number	Age (years)	Time since gastrostomy (years)	Removal by
1	7	5	Interventional Radiology
2	3	2	Laparoscopy
3	4.5	0.58	Laparotomy
4	9.25	0.5	Laparotomy
5	3.75	2.5	Laparoscopy
6	4.75	3.42	Laparoscopy
7	15.2	2.5	Endoscopic
8	5.25	3.92	Laparotomy
9	12	2.1	Laparotomy
10	4.75	3.5	Endoscopy
11	12	3.25	Endoscopy

Patient number	Age (years)	Time since gastrostomy (years)	Removal by
12	18	3	Laparotomy
13	5.83	2.83	Laparotomy
14	2.83	1	Endoscopy
15	9.25	1.25	Laparotomy
16	4	1.42	Laparotomy
17	3.25	0.75	Laparotomy
18	7	3	Laparotomy
19	12.34	0.08	Laparotomy
20	5.6	3.84	Laparotomy

Table 3-1 Patient's age, time since gastrostomy and method of removal

There were 2,007 patients who underwent percutaneous gastrostomy insertion. Over the time period twenty children (11 boys) were found to have

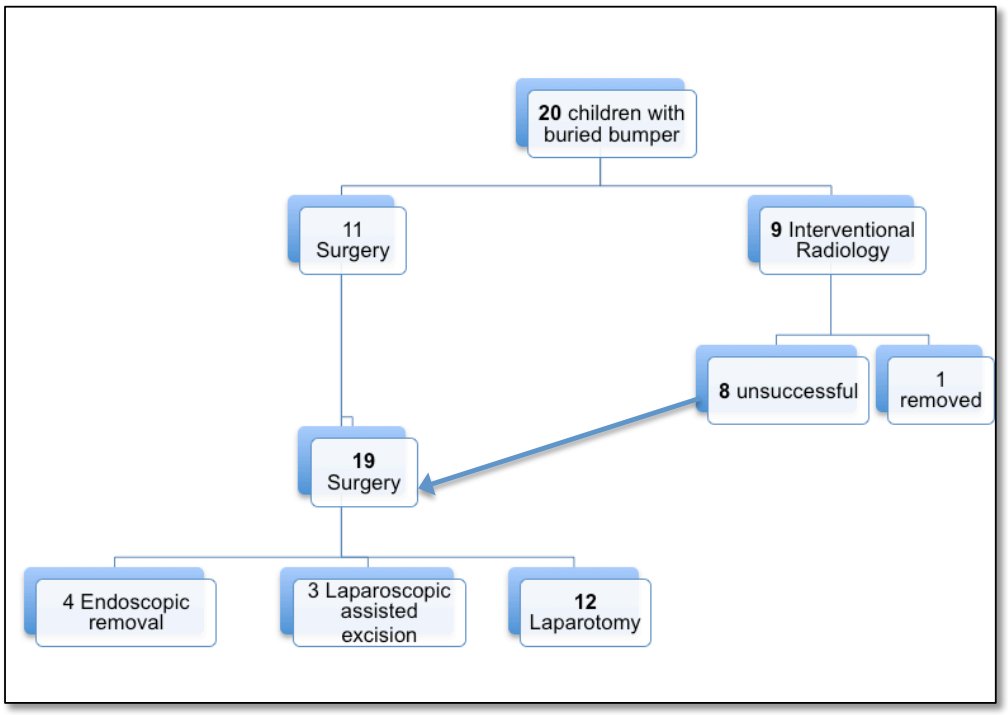


Figure 3-2 Management of buried bumpers

a buried gastrostomy. Six children had a Freka gastrostomy with jejunal extension. Most of them (n=14) had underlying neurological condition. Three had a metabolic disorder and three, an endocrine disorder.

The median age at presentation was 5.75 years (2.83 - 18 years). They presented at a median of 2.5 years (1 month - 5 years) after gastrostomy insertion (Table 3-1). Half of the children (n=10) presented with symptoms related to buried bumper which included leakage around the gastrostomy (n=4), pus, discharge or bleeding from the site (n=5), stiffness on feeding (n=3) and unable to push the flange (n=1). There were 3 children with more than one symptom. The other half (n=10) were asymptomatic and were booked for routine change or removal of gastrostomy. In nine children there was an attempt to remove the flange by interventional radiology but this was successful only in one. A snare was inserted through the catheter hole, under fluoroscopic guidance and the bumper was removed through the oesophagus (Turner and Deakin, 2009). In the remaining 19 children, 4 had endoscopic removal while 15 children developed an inflammatory mass and required a laparotomy (n= 12) or laparoscopic assisted excision (n= 3) (Figure 3-2). The four endoscopic removals included two removed by external traction against the abdominal wall. In the remaining two the flange was removed by pushing it from the wall of the stomach towards the lumen. To facilitate this, a metal probe was inserted into the shortened gastrostomy tube from outside, stiffening it and allowing the flange to be pushed into the gastric lumen (Figure 3-3). This was then retrieved by a snare; thus avoiding an open procedure.

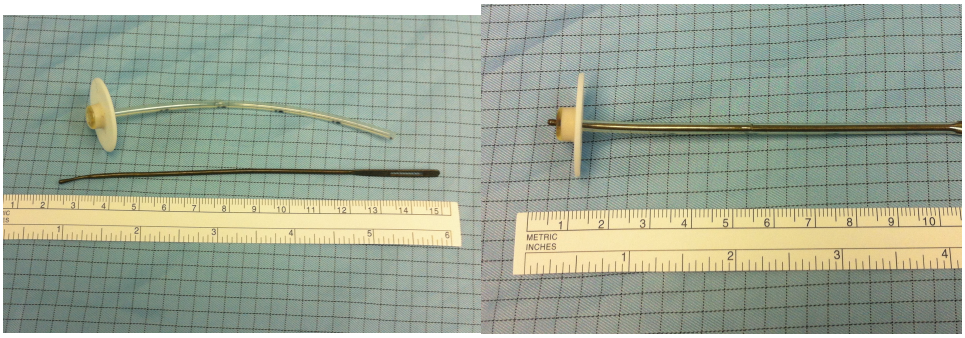


Figure 3-3 A metal probe inserted into the shortened gastrostomy tube from outside

The patients were followed up for 12 months (1-45 months). There were two complications (10%). One had a gastrostomy site infection and another an abscess of the old gastrostomy site, each needing oral antibiotics.

3.4 Discussion

Buried bumper has been described in the adult literature to potentially cause perforation of the stomach, peritonitis and death (Anagnostopoulos et al., 2003). The commoner presenting symptoms of difficulty in infusing feeds, pain and peri-tubular leak might not be picked up initially, especially in the neurologically impaired child with difficult communication.

The true incidence of buried bumper cannot be estimated by this study. This was a retrospective study and often the patients would go back to heir local hospital for follow up. In case of emergency presentation due to the buried bumper they could be taken to their local paediatric surgery hospital. Therefore, data for the true incidence of buried bumpers could not be captured. Even when the patients came back for follow up in our hospital, they did not undergo planned endoscopy and change to a balloon gastrostomy device at the recommended 3 months post gastrostomy tube insertion (Heuschkel et al., 2015).

The diagnosis can be made by the history and occasional palpation of the gastrostomy flange below the skin, with or without pain (Khalil et al., 2010). However, in our series palpation did not reveal the buried bumper, which was retained in the stomach wall. Radiological investigations such as ultrasound or computerized tomography can be useful (Hodges et al., 2001, Khalil et al., 2010). However, the confirmation is made by endoscopy, which shows a mound of gastric mucosa, with minimal or absent visible gastrostomy disc.

The two most widely used gastrostomy devices in the UK are Freka and Corflo gastrostomy. A recent study attributes the hard, thin internal bumper of Freka gastrostomy to predispose to buried bumper. In comparison their experience with the Corflo gastrostomy tube which has a thicker, cushioned internal bumper showed less incidence of buried bumpers (Dowman et al., 2015) Figure 3-4. There are studies which associate this complication with a rigid or semi-rigid internal fixation device and rarely to a balloon secured device (Kim et al., 2006, Lee and Lin, 2008). Conversely, there has been

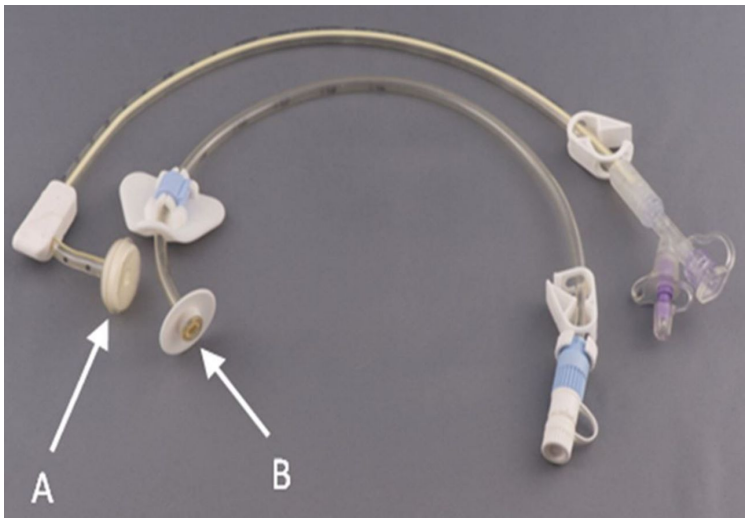


Figure 3-4 Corflo and Freka percutaneous endoscopic gastrostomy (PEG) tubes.

The inner bumper on the Corflo (purple) PEG tube (A) is thicker and spongier compared with the thin and flat Freka (blue) inner bumper (B)

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report of a buried gastrostomy balloon device (Smith and Goday, 2008). There are gastroenterologists and surgeons who believe in inserting a balloon device rather than a device with an internal bumper to avoid this complication. However a primary balloon secured device has a high risk of causing severe morbidity and possible mortality if the balloon gives way and the stomach separates from the anterior abdominal wall in the first few months post insertion, before the gastrostomy tract has formed and matured.

Factors implicated in the development of buried bumper are excessive tension between the inner and outer flange of the gastrostomy, causing pressure necrosis of the gastric mucosa, leading to its migration into the abdominal wall and inadequate gastrostomy care (Hodges et al., 2001, Khalil et al., 2010).

In a telephonic interview 15 (75%) parents /carers were not pushing the gastrostomy tube and rotating it, as is our present recommendation. Four parents could not be contacted and unfortunately, one child had died due to advanced primary disease. The NICE (National Institute for Health and Clinical Excellence) guideline for gastrostomy care in adults recommends weekly tube rotation to prevent internal over-granulation or buried bumper syndrome (2006). In children, the rotation of the tube should be associated with advancement of the flange at least once a week to avoid migration of the bumper into the wall of the stomach, as the child grows. There is increased incidence of buried bumpers in children with PEG with jejunal extension (Goring et al., 2016, Stewart et al., 2017). Although the device cannot be rotated, it should be advanced into the stomach.

Various approaches have been suggested for the removal of the buried bumper. These include external traction, endoscopic, laparotomy, radiological-guided and laparoscopic excision (Khalil et al., 2010, Ehsan et al., 2012, Furlano et al., 2008, Kohler et al., 2008, Binnebosel et al., 2010,

Hodges et al., 2001, Segal et al., 2001, Turner and Deakin, 2009). In the suitable patient endoscopic submucosal dissection using HybridKnife (Curcio et al., 2014) or single-step endoscopic procedure using an 18-mm oesophageal balloon dilator to extract the bumper through the stomach and mouth can be used (Christiaens et al., 2014). Our experience in an uncomplicated buried bumper i.e. without an inflammatory mass favours endoscopic-guided removal. In children with an inflammatory mass, laparoscopic-assisted excision facilitates dissection, minimises tissue disruption and should be the first choice. Radiological-guided removal of a buried gastrostomy in children is rarely successful and requires an experienced interventional radiologist.

3.5 Conclusions

Buried bumper is an uncommon, serious complication of one of the commonest procedures in children. This can be avoided by proper gastrostomy care. Endoscopic removal should be the first line of treatment, failing which a laparoscopic assisted excision or laparotomy is recommended.

3.6 Recommendations

It is advised that a prospective registry is maintained to keep track of all gastrostomy tube inserted. They should be assessed by at least 3 months post insertion and a plan to either change to a balloon secured gastrostomy device or removal be made with the parents/carers. The morbidity associated with a buried bumper is great and if the underlying medical condition prevents this, then the child should have an endoscopy and change of the device no later than 2 years after insertion of the gastrostomy tube.

Chapter 4 Surgical Jejunostomy and radiological gastro-jejunal tube feeding in children: Risks, benefits and nutritional outcomes

4.1 Background

In children with gastrointestinal dysfunction, jejunal access can be used for enteral feeding. The inability to tolerate gastric feeding can be due to gastro-oesophageal reflux, gastric dysmotility and poor gastric compliance (Raval and Phillips, 2006). Historically, these children received a surgical jejunostomy (SJ). Radiologically inserted gastro jejunal tubes (RGJ) are now more commonly used than surgical jejunostomy (Hoffer et al., 1999, Wales et al., 2002).

I reviewed outcomes in children with surgical feeding jejunostomy and radiologically inserted trans-gastric jejunal feeding tubes at my institute.

4.2 Methods

After appropriate institutional audit approval (no. 1035), a retrospective review to identify patients who had a jejunostomy in the year 2010 was performed. I reviewed the hospital coding database and identified seventy-eight children who had a jejunostomy in 2010. Of these, 29 children were excluded as detailed notes review revealed that they either did not have the primary jejunostomy in 2010 or the jejunostomy was a part of laparotomy to act as a de-functioning stoma. I extracted data on outcomes from those with a ‘de novo’ RGJ or SJ from clinic and discharge letters, admission records, imaging procedures and inpatient stay records. Procedures were performed by consultant interventional radiologists or paediatric surgeons; or by trainees at specialist registrar level under direct supervision of a consultant.

I compared RGJ and SJ patients with respect to demographic data, neurological diagnosis, indication, previous anti-reflux surgery, complications, hospital admission, further surgery, removal of the device and follow up. I reviewed their weights before and after RGJ or SJ as an outcome measure. Weight-for-age Z scores (Standard deviation scores)

were calculated using the LMS growth add-in (Cole and Pan, 2011) for Microsoft Excel 2010 (Microsoft Corporation) program, using British 1990 reference data (Cole et al., 1998). A Z-score of 0 is equivalent to 50th centile, -1 to 16th centile and -2 to 2nd centile. Malnourished children were defined weight Z-score of -2 or less. Growth over time was assessed as mean change in Z-score per year by Multilevel modelling using MlWin 2.36 (Centre for Multilevel Modelling, University of Bristol, Bristol, UK).

4.3 Results

Forty-eight children had access for jejunal for feeding in the year 2010 and they were included in the study. Demographic data are presented in Table 4-1. More than half of the patients who received either RGJ or SJ were

	RGJ (n=36)	**SJ (n=12)**
Age median (range) in months	37 (5-202)	41 (6-213)
Sex	17 males/ 19 females	11 males/ 1 female
Neurological impairment	21 (58%)	8 (67%)
Other indications - Gastric dysmotility associated with:	Metabolic disorder 3 Oesophageal atresia 2 Failure to thrive 2 Cardiac disorder 2 Malignant disorder 2 Endocrine disorder 1 Dystrophic epidermolysis bullosa 1 Short bowel syndrome after resection for multiple atresia 1 Severe combined immune deficiency 1	Oesophageal atresia 1 Gut failure due to immune dysregulation 1 Metabolic disorder 1 Endocrine disorder 1

Table 4-1 Demographic data of children receiving a jejunostomy in 2010.

neurologically impaired (58% and 67% respectively). Indications for jejunal feeding are listed in Table 4-2 In 83% of SJ and 69% of RGJ it was recurrent gastro-oesophageal reflux. This was confirmed by either a contrast study, or pH study. The majority of children in each group had a previous anti- reflux operation n=19/36 (53%) in RGJ and n=612 (50%) in SJ (Table 4-3).

	RGJ (n=36)	**SJ (n=12)**
Recurrent GOR	25(69%)	10(83%)
Not tolerating gastric feeds	11(31%)	0
Duodenal obstruction due to: Multiple intestinal strictures	0	1(8%)
Long gap Oesophageal atresia: Gastric pull up + SJ	0	1(8%)

Table 4-2 Indications for jejunal feeding

GOR = Gastro-oesophageal reflux

	RGJ (n=36)	SJ (n=12)
Previous surgery n (%)	Fundoplication +G 15 (42) Gastrostomy 12 (33) Fundoplication + Revision + G 4 (11) None 5 (14)	Fundoplication + G 5 (42) Gastrojejunostomy 4 (33) Laparotomy 3 (25) Gastrostomy 3 (25) Fundoplication + Revision twice+G 1 (8) None 1 (8) (n=4 had more than 1 procedure)
Further surgery n (%)	Revision Fundoplication + G 6 (17) SJ 4 (11) Removal of buried bumper 3 (8) Fundoplication + G 2 (6) Revision of G 3 (8) (n=3 had more than 1 procedure)	Re-fashioning 2 (17) Laparotomy (bowel obstruction) 2 (17)

Table 4-3 Previous surgery and further surgery after a RGJ or SJ

G = gastrostomy

The type of surgical jejunostomy depended on the choice of the operating surgeon and the disease aetiology. Most of the surgeons preferred formation of Roux-en-Y jejunostomy (Table 4-4).

Type of SJ :	
Roux-en-Y	n=7
Witzel tunnel	n=4
Laparoscopy-assisted	n=1

Table 4-4 Type of surgical jejunostomy.

There were 4 major complications in each of the RGJ (11%) and SJ (33%) groups (Table 4-5).

Complications (n=8)		
RGJ (n=4)	Buried bumper	
SJ (n=4)	Bowel obstruction (n=2)	Colon volvulus and ventral hernia at fundoplication site (roux-en-Y SJ, n=1)
		Intussusception and small bowel volvulus (tunnel SJ, n=1)
	Re-fashioning of SJ due to stenosis/atresia (n=2)	

Table 4-5 Complications after RGJ and SJ.

The RGJ group needed tube replacement 1.3 (0-20) times/year. Fifteen needed further operation (Table 4-3). In 20/36 children, RGJ was removed after 0.8 years (0.1-2.4). Four were fed orally, 3 oral with gastrostomy, 5 via gastrostomy alone, 5 had fundoplication plus gastrostomy and 3 converted to SJ.

Twelve children had SJ (Table 4-4), which was a part of laparotomy in 5/12. Four (33%) had SJ after RGJ. SJ was reversed in one orally fed child.

Nutritional outcome was measured as weight Z-scores over time. RGJ children were on average slightly underweight (mean -1.4 ± standard error 0.26 Z-scores) at jejunostomy, with 4/36 (11%) of children malnourished (less than -2 Z-scores) SJ children were on average significantly malnourished (-3.7±0.99 Z-scores) at the time of jejunostomy, with 4/12 (33%) of children less than -2 Z-scores. RGJ children grew stably (+0.4±0.1 Z-scores per year FU, p=0.58) and growth significantly improved following SJ (+1.2±0.3 Z-scores/year FU, p<0.0001) (Figure 4-1 and Figure 4-2).

RGJ were followed up for a median of 2.4 (0.18-3.4) years, while SJ were followed up for a median of 1.8 (0-3.5) years.

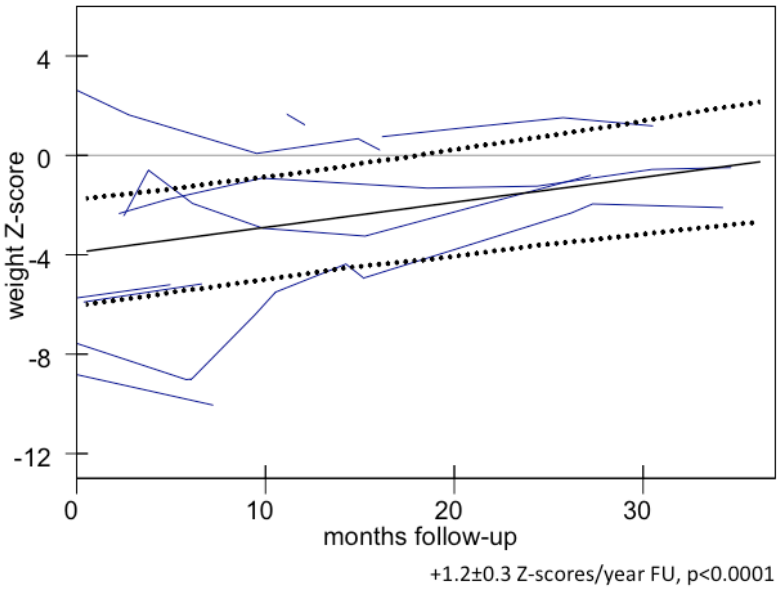


Figure 4-1 Weight Z scores for children after SJ.

Individual patients are shown together with the mean trend line with 95% confidence intervals of the mean, analysed by multilevel modelling.

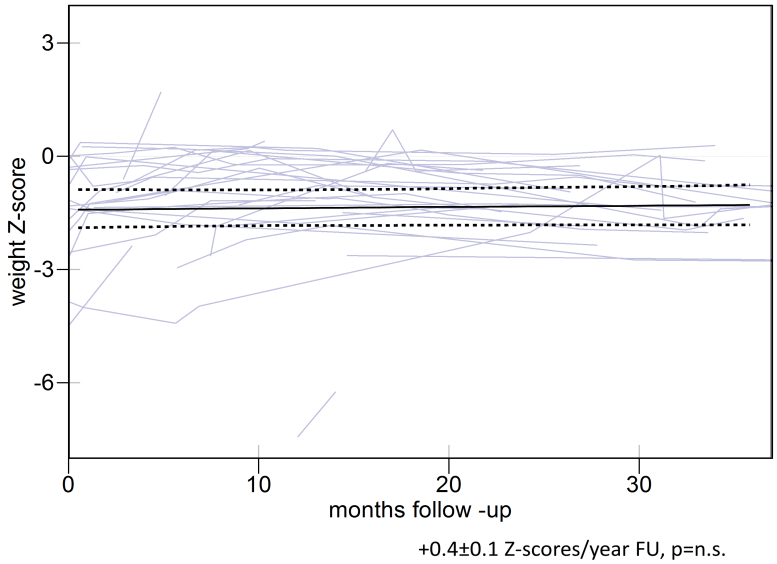


Figure 4-2 Weight Z scores for children after RGJ.

Individual patients are shown together with the mean trend line with 95% confidence intervals of the mean, analysed by multilevel modelling.

4.4 Discussion

Following the PEG vs. RIG trial the next logical step would be to compare RGJ and percutaneous endoscopic gastrojejunostomies. However, percutaneous endoscopic gastrojejunostomies were not performed at my institution.

Complex, neurologically impaired children have a range of feeding difficulties from uncoordinated swallow to GORD and gastrointestinal dysmotility. Once maximal medical therapy has failed management options include gastric tube feeding, anti-reflux procedure, jejunal feeding or a combination. The rate of recurrent GORD after an anti-reflux procedure is between 10-14% (Lopez-Fernandez et al., 2014, Rossi et al., 2016, Wheatley et al., 1991). For these patients a re-do fundoplication has a high failure rate of 20-30% (Kimber et al., 1998, Furnee et al., 2008). Jejunostomy feeding has been previously reported and may be preferred over a redo fundoplication (Albanese et al., 1993, Wales et al., 2002). Long term outcomes following SJ and RGJ have been compared in a previous series (Raval and Phillips, 2006). They concluded that SJ are more stable feeding access devices with fewer complications.

There is a reported association of buried bumpers and gastro-jejunal tubes (Goring et al., 2016) (when the gastric component of the tube is inserted as a percutaneous technique). This can be due to reluctance of the carer to advance the gastro-jejunal device, for fear of dislodging the jejunal component. Due to presence of the jejunal tube the carers are advised to only advance the gastrostomy tube and not to rotate it. Often the jejunal component of the RGJ is routinely replaced and the gastrostomy device remains in situ for a longer duration than intended.

The children who received a SJ had various rare disease pathologies. One child had multiple intestinal abscesses as a part of global immune deficiency. He had multiple resections and anastomoses of the small bowel during formation of SJ. There was stenosis of the jejunostomy later as a part of the disease process and it required revision. Another child with congenital myopathy and oesophageal stricture, developed stenosis of the stoma mouth and needed re-fashioning of the jejunostomy. There were two children who developed small bowel obstruction due to adhesions (Table 4-5).

SJ have been reported to have a high complication rate (Table 1-2). Williams et al reported major complication rate of 37% (Williams et al., 2007) and Smith et al reported a major complication rate of 31% (Smith and Soucy, 1996) with roux-en-Y SJ. Taylor et al reported volvulus around roux-en-Y SJ in 5 out of 25 patients (20 % complication rate) (Taylor and Ryckman, 2010). Egnell et al reported 33% re-operation rate after SJ for small bowel obstruction, perforation, wound rupture tube dislodgement and tube leak (Egnell et al., 2014). At my institute the surgical technique has evolved over time, with roux-en-Y SJ, having a shorter stem of the roux-en-Y limb, thus minimizing the risk of volvulus.

Determining nutritional benefit from RGJ or SJ in this complex group of children is challenging. The use of weight Z-scores before and after the jejunostomy insertion gives an objective measure of the probable effect of the intervention on nutrition. As the underlying disease progresses, becomes stable or regresses, there may be an effect on absorption of nutrients from the gut and maintenance of nutrition. Changes in z scores are multi factorial and includes changes in feeding regime, formulas used, and other background general illness. The patients who had an RGJ were slightly underweight at the start and maintained stable weight gain (manifested as stable Z-score). The patients who had a SJ on the other

hand were significantly malnourished at SJ insertion and their growth improved significantly (significant increase in weight Z-score). Rather than just the effect of the jejunostomy this result reflects the fact that patients who had a SJ had the jejunostomy after progressive deterioration of the primary disease and failure of escalating nutritional interventions. Given our data, we conclude that both RGJ and SJ are effective as they have a stabilizing effect on reliable delivery of nutrition.

Another aspect that requires consideration in the choice of procedure to be offered is the radiation dose received, not just at the initial RGJ insertion, but also each time the tube is replaced. In a sample of 110 consecutive patients (not the same patients as the primary study population, as data were not available) the median radiation dose-area product (DAP) for a change of RGJ tube was 7 μGy·m^2 (0-622 μGy·m^2, Figure 4-3) with a median fluoroscopy time of 25 s (0s-40min). There is no clear consensus regarding the additional cumulative lifetime risk of radiation to patients (Andronikou, 2017).

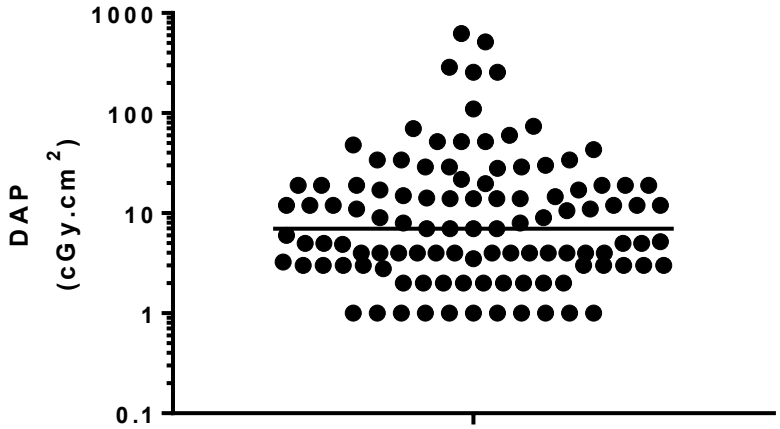


Figure 4-3 Dose area product (DAP) for 110 children having an RGJ tube change

Horizontal line denotes the median DAP

The average cost of insertion of a SJ is around £11,000 as the procedure involves a general anaesthetic, theatre time and in patient stay of several days (although several SJ patients had SJ insertion together with another abdominal procedure), whereas the average cost associated with a day case admission and insertion of RGJ in the radiology suite is around £590 (data obtained from the hospital costings department). The recurrent costs associated with each is also likely to be different: RGJ will require changing in IR approximately every 6 months, whereas the SJ tube can be replaced in an outpatient appointment. A full cost-effectiveness analysis, including the cost of complications, however was not undertaken as part of the current study.

In the adults laparoscopic jejunostomy has been reported in 299 patients with low rate of post-operative small bowel obstruction (Young et al., 2016). Laparoscopic roux-en-Y jejunostomy has been reported in 5 children one of whom required dilatation for stomal stenosis (Neuman and Phillips, 2005). Esposito et al have described laparoscopic assisted jejunostomy formation in ten neurologically impaired children (Esposito et al., 2013). One patient (10%) died one year after the procedure of unknown causes. The other complications were four (40%) peristomal hernias, two (20%) device dislocation and 1 peristomal granuloma.

Direct percutaneous endoscopic jejunostomy has been reported in five children with good results (Virnig et al., 2008). However in a large series of 286 adult patients, the success rate was 68% and the procedure was associated with a complication rate of 10% (Maple et al., 2005). Recently percutaneous laparoscopic endoscopic jejunostomy has been reported in sixteen children (Belsha et al., 2016). They had two complications (12.5%) of small bowel volvulus, which required surgical intervention.

The effect of repeated hospital admission for RGJ tube replacement with inadvertent displacement on the quality of life of the patient and caregivers has not been studied in the adult or paediatric literature. However, we believe that this remains an important factor in their overall care.

Although there are papers citing increased morbidity after a RGJ (Fortunato et al., 2005, Godbole et al., 2002), this remains a feasible alternative in the fragile patient with compromised respiratory function due to recurrent aspiration (Karabulut et al., 2015).

4.5 Conclusions

It is not intended to directly compare SJ and RGJ, as this group of patients represent a heterogeneous population who often have had a trial of nasogastric, gastric, naso-jejunal, RGJ feeding before becoming significantly malnourished, thus resorting to a SJ as a rescue procedure. Although RGJ require more device maintenance than SJ, they have less severe complications. RGJ can be used as a temporary stabilizing measure after failed anti-reflux operations in the neurologically impaired. Insertion or replacement through an existing gastrostomy under radiological guidance obviates the need for a general anaesthetic in most cases. The complications after a SJ although less, can be life threatening and may require an emergency laparotomy under a general anaesthetic. SJ is a definitive long-term feeding device.

A consistently high DAP for tube changes in an individual patient might be a relative indication to convert from a RGJ strategy to SJ. The cost and inconvenience associated with tube replacement and hospital admission is another important consideration. This information should be presented to the family while counselling for the choice of jejunal tube. They should be able to make an informed decision along with the clinician.

RGJ and SJ are important tools for nutritional management that achieve and maintain growth in a complex group of children. The risk and benefits should be reviewed for each individual patient.

4.6 Recommendations

A well designed prospective randomised controlled trial, with a sample size to detect a difference in complications/outcomes after anti-reflux operation or gastro-jejunal tube feeding in neurologically impaired children is needed. A formal quality of life assessment for the patient and caregivers is also needed.

Chapter 5 A comparison of three scoring systems to assess complications in a prospectively collected patient sample

5.1 Aim of the study

To compare different scoring systems, for documenting outcomes, complications and morbidity after a surgical procedure.

5.2 Methods

A prospectively collected dataset of post-operative complications for two cohorts of patients were analysed according to the well-established Clavien-Dindo classification (Dindo et al., 2004) (see Chapter 1.6.3), the newer Comprehensive Complication Index (Slankamenac et al., 2013) (see Chapter 1.6.4) and the PEG vs. RIG Complication score (see Chapter 2.4.7).

5.2.1 Clavien-Dindo Classification

The treatment used to correct the complication after a surgical procedure is the basis of this classification. It consists of seven grades (I, II, IIIa, IIIb, IVa, IVb and V) Table 1-3. It aims to eliminate reporting bias by including objective criteria, which are well documented and unambiguous.

5.2.2 Comprehensive Complication Index (CCI)

Rather than focussing on the most severe complication post-operatively, the CCI takes into account all the adverse events and gives a thorough account of the post-operative course. The developers have made readily accessible the CCI®-Calculator, which is an online tool for the assessment of postoperative complications and calculation of the CCI® in one single patient as well as in a group of patients. It is validated in adults but not in children.

5.2.3 PEG vs. RIG Complication Score

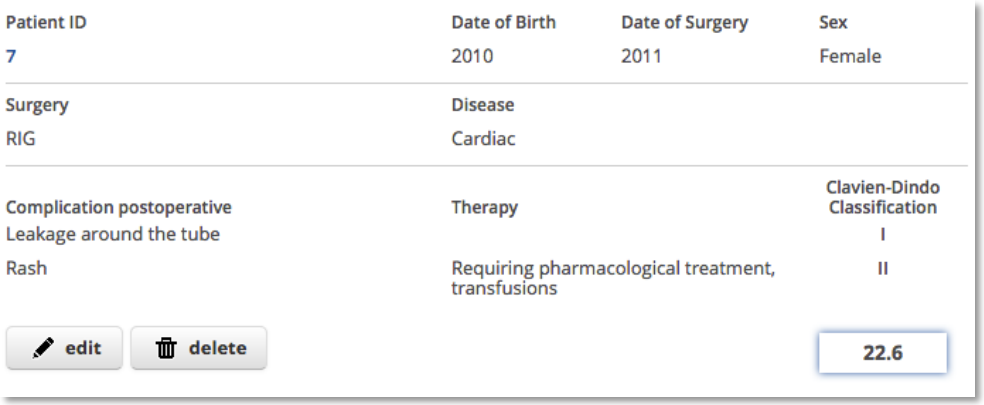
Although the above scoring systems have been validated in adults, no validation has taken place in children. A direct comparison of complications can be misleading as the complications seen vary widely in severity. For instance, some published reports of minor complications took only wound site problems into account (Barron et al., 2000), while other reports also included delayed feeds and tube-related issues (Friedman et al., 2004, Malden et al., 1992). In addition, some patients may experience more than a single complication. Thus, we devised a gastrostomy complication scoring system specific for children, where complications were ascribed scores weighted for severity. We believe that the total score per patient is a more accurate reflection of the success of the procedure. The score was devised in a consensus meeting attended by experts in the field (paediatric surgeons, interventional radiologists, junior doctors and nurses, Table 2-2). However, this score is not validated.

5.3 Results

The scores according to each of the three systems for each patient in the PEG vs. RIG trial were calculated. A few sample patients are described below (Clavien-Dindo classification followed by CCI using, the CCI®-Calculator and then the PEG vs. RIG complication score).

Patient 7

Clavien-Dindo Classification: II



Patient ID	Date of Birth	Date of Surgery	Sex
7	2010	2011	Female

Surgery	Disease
RIG	Cardiac

Complication postoperative	Therapy	Clavien-Dindo Classification
Leakage around the tube		I
Rash	Requiring pharmacological treatment, transfusions	II

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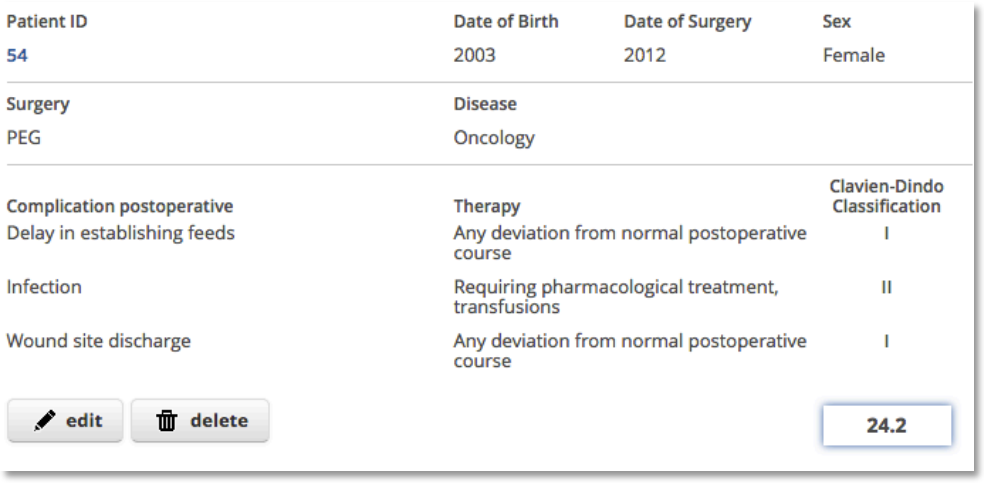
22.6

PEG vs. RIG score: 4

Patient 54

Clavien-Dindo Classification: II



Patient ID	Date of Birth	Date of Surgery	Sex
54	2003	2012	Female

Surgery	Disease
PEG	Oncology

Complication postoperative	Therapy	Clavien-Dindo Classification
Delay in establishing feeds	Any deviation from normal postoperative course	I
Infection	Requiring pharmacological treatment, transfusions	II
Wound site discharge	Any deviation from normal postoperative course	I

edit delete

24.2

PEG vs. RIG score: 3

Patient 18

Clavien-Dindo Classification: II

Patient ID	Date of Birth	Date of Surgery	Sex
18	2010	2012	Male

Surgery	Disease
PEG	Gastrointestinal

Complication postoperative	Therapy	Clavien-Dindo Classification
Infection	Requiring pharmacological treatment, transfusions	II
Delay in establishing feeds	Any deviation from normal postoperative course	I
Granulation	Any deviation from normal postoperative course	I
Wound site discharge	Any deviation from normal postoperative course	I
Migration	Any deviation from normal postoperative course	I
Leakage	Any deviation from normal postoperative course	I
Infection	Requiring pharmacological treatment, transfusions	II
Infection	Requiring pharmacological treatment, transfusions	II
Wound site discharge	Any deviation from normal postoperative course	I
Breakage	Any deviation from normal postoperative course	I
Pulled out	Any deviation from normal postoperative course	I
Leakage	Any deviation from normal postoperative course	I
Breakage	Any deviation from normal postoperative course	I
Wound site discharge	Any deviation from normal postoperative course	I
Granulation	Any deviation from normal postoperative course	I
Wound site discharge	Any deviation from normal postoperative course	I
Leakage	Any deviation from normal postoperative course	I

edit delete

48.6

PEG vs. RIG score: 26

Patient 75

Clavien-Dindo Classification: 0

Patient ID	Date of Birth	Date of Surgery	Sex
75	2011	2012	Female

Surgery	Disease
PEG	Oncology

Complication postoperative	Therapy	Clavien-Dindo Classification
None	No complication	0

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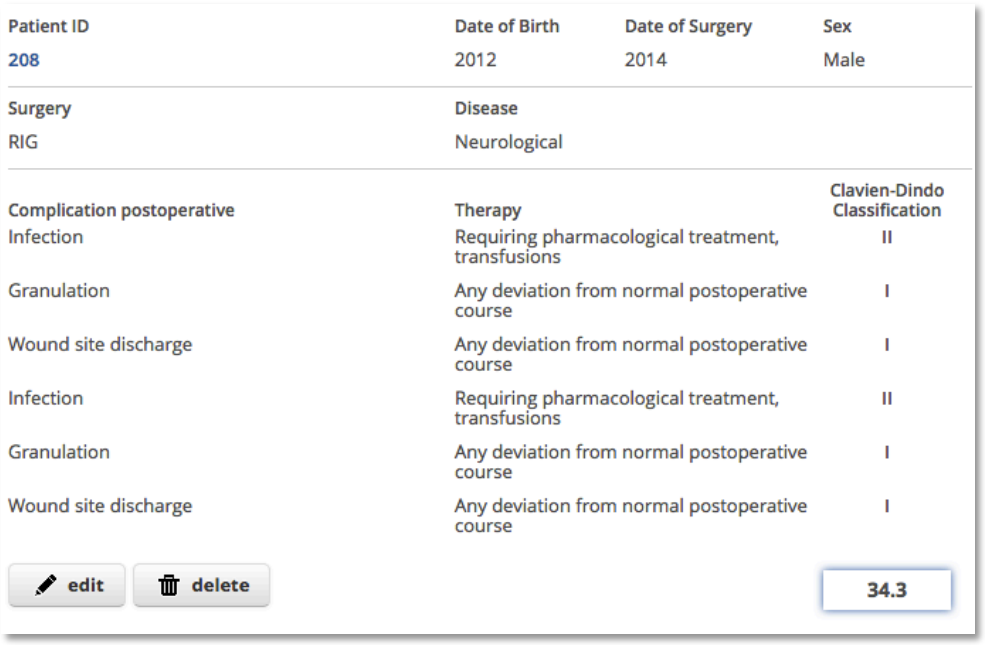
0.0

PEG vs. RIG score: 0

Patient 208

Clavien-Dindo Classification: II



Patient ID	Date of Birth	Date of Surgery	Sex
208	2012	2014	Male

Surgery	Disease
RIG	Neurological

Complication postoperative	Therapy	Clavien-Dindo Classification
Infection	Requiring pharmacological treatment, transfusions	II
Granulation	Any deviation from normal postoperative course	I
Wound site discharge	Any deviation from normal postoperative course	I
Infection	Requiring pharmacological treatment, transfusions	II
Granulation	Any deviation from normal postoperative course	I
Wound site discharge	Any deviation from normal postoperative course	I

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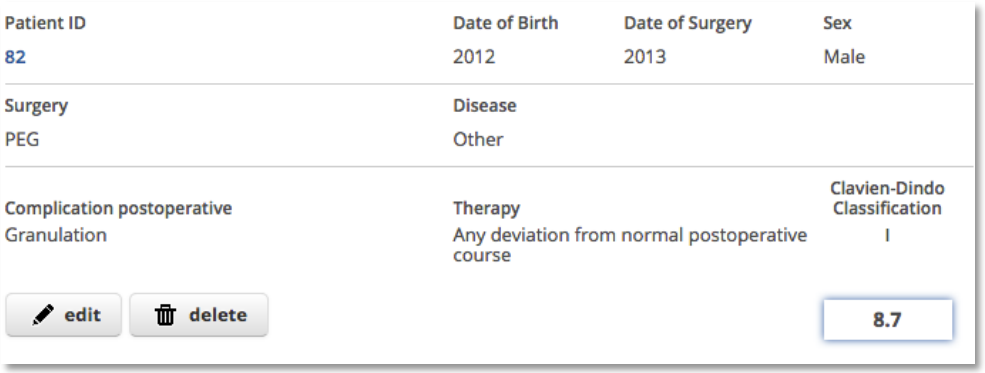
34.3

PEG vs. RIG score: 6

Patient 82

Clavien-Dindo Classification: I



PEG vs. RIG score: 1

5.4 Discussion

The prospectively collected post operative complications for patients in the PEG vs. RIG trial was analysed using the three scoring systems. The relationship between scores was analysed using linear regression; the PEG vs. RIG complication scores and the CCI show a significant positive relationship (Figure 5-1).

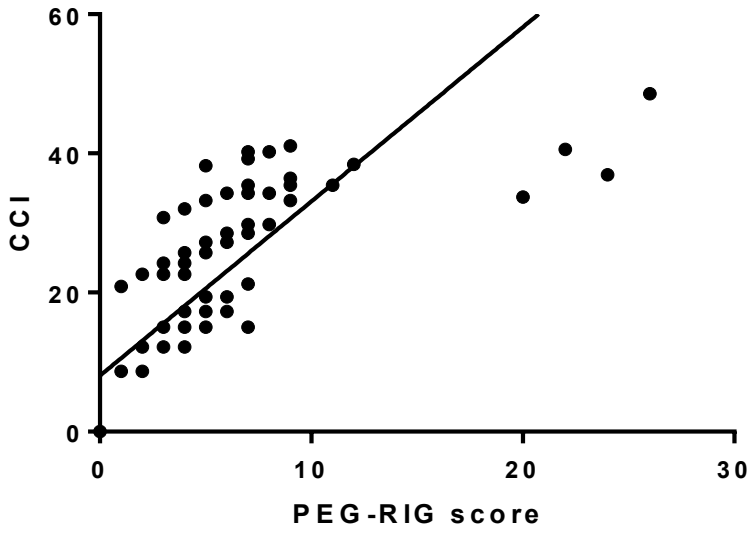


Figure 5-1 Linear regression analysis of CCI against PEG vs. RIG score

R^2=0.59, P<0.0001

If the four outliers with a PEG vs. RIG score of more than 20 are removed (Table 5-1), the linear relationship becomes stronger (Figure 5-2). There were 2 patients each with a PEG and RIG. Patient 71 had a gastro-colic fistula, which required a laparotomy 10 days later for closure of the fistula and re-siting of gastrostomy. Patient 131 developed an abscess, which needed aspiration under a general anaesthetic. Both these patients have a high PEG vs. RIG score and CCI score. Patient 17 had a buried bumper, which required a general anaesthetic. Patient 18 had severe gastro-oesophageal reflux and had multiple problems with infection, discharge, leakage and granulation tissue, none requiring a general anaesthetic.

Patient ID	PEG/RIG	PEG vs. RIG	CD	CCI
71	RIG	20	3	33.7
131	RIG	22	3	40.6
17	PEG	24	3	36.9
18	PEG	26	2	48.6

Table 5-1 Comparison of scores for patients with PEG vs. RIG score greater than 20

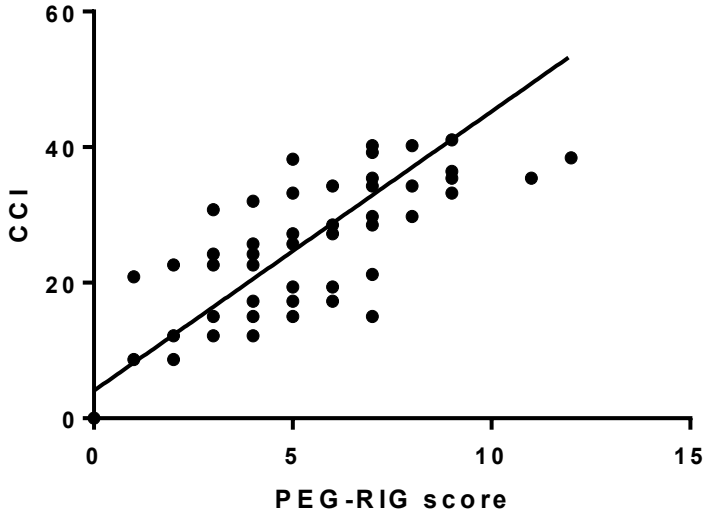


Figure 5-2 Linear regression analysis of CCI against PEG vs. RIG score without outliers

R^2=0.76, P<0.0001

There were 7 patients (Table 5-2) with high CCI of more than 40 and low PEG vs. RIG score (between 7-9). These patients had multiple episodes of infection and wound site discharge. They required antibiotics which score a

higher score on CCI and Clavien-Dindo grade, whereas on the PEG vs. RIG score, these are only classed as minor complications, with a score of 1. This highlights the potentially subjective nature of these scoring systems, and also possibly differences in clinician perception of severity of complication between adults (CCI and Clavien-Dindo) and children (PEG vs. RIG score).

Patient ID	PEG/RIG	PEG vs. RIG	CD	CCI
10	PEG	7	2	40.2
21	PEG	7	2	40.2
112	RIG	7	2	40.2
176	RIG	7	2	40.2
195	PEG	7	2	40.2
104	PEG	8	2	40.2
69	RIG	9	2	41.1

Table 5-2 Comparison of scores for patients with CCI score greater than 40

5.5 Conclusions

In general, the well-validated CCI scoring system in adults closely mirrors the PEG vs. RIG scoring system. The PEG vs. RIG scoring may be a suitable indicator for this group of patients, as it is specific for the operation they underwent. However, a scoring system, which is specific for the paediatric population undergoing any surgery, is much needed, especially in an era when publication of surgical outcome data is mandated.

Chapter 6 Paediatric complexity index: preliminary study of a novel tool to measure morbidity in the paediatric surgical patient

6.1 Background

In 1911, Ernest Codman after being ostracised from Massachusetts General Hospital in Boston opened the 'End Result Hospital'. He focussed on the End Result system, which in his words was, *"The common sense notion that* every *hospital should follow* every *patient it treats, long enough to determine whether or not the treatment has been successful, and then to inquire, 'If not, why not?' with a view to preventing similar failures in the future"* (Brand, 2009). He followed each patient up for at least a year and made public any complication they had, to improve future care. He believed that the patient should be able to make an informed decision about his/her treatment. He advocated that this system should be used to judge surgeons and determine promotions, rather than seniority. A hundred years ago he was well ahead of his times and was disliked by many of his colleagues.

More recently, closer to home, Professor Sir Ian Kennedy who chaired the public enquiry into the high number of deaths after cardiac operations in babies at the Bristol Royal Infirmary (Smith, 1998), recommended that clinical teams should publish their results as individuals and as hospital units. The manner in which this information is collected and analysed remains controversial. There is widespread scepticism amongst the various surgical specialities about the susceptibility of misinterpretation by the media and public. However, despite this the Society for Cardiothoracic Surgery in Great Britain and Ireland (SCTS) has been publishing their outcome statistics for NHS hospitals and individual surgeons on their website since 2005 - accessed (2017). Their intention was to reinstate the public's confidence as well as to provide a means for constructive feedback to individual surgeons and units.

The Royal College of Surgeons encourages the publishing of individual outcome data onto the public domain such as NHS Choices. They have

provided consultant specific outcome data for 28 commonly performed operations for more than 5,000 consultant surgeons in the UK. Such data is important for individuals' appraisal and revalidation as well. However, there is no such data for any paediatric surgical procedures. Recently there has been an initiative by the British Association of Paediatric Surgeons to enter consultant outcome data for two specific paediatric surgical conditions - hypospadias and gastroschisis. Currently this is voluntary, however participation in the database is a pre-requisite for revalidation. The data will be cross-checked against the Hospital Episodes Statistics data (UK) and ISD (Scotland). There is a need for risk stratification especially in complex operations with a very complex case mix of background conditions. Risk stratification is important for the following reasons (Keogh et al., 1998):

1. So as not to judge individual surgeons performing high-risk procedures in complex patients unfairly against those performing the same procedures in otherwise 'well' patients.

2. So that the high-risk patients are identified beforehand and a fully informed pre-operative consent can take place. The information will also help mitigate the reluctance of the surgeon to operate in these high-risk cases for fear of being penalised.

3. So that the often overlooked influences of medical management and referral, anaesthetic care and intensive care resources can be accounted for. This can help build the case for improvement of facilities and support where necessary.

The importance of accurate risk stratification is highlighted by the recent media controversy regarding results and potential closures of paediatric cardiac surgical centres. Although progress has been made in risk stratification for predicting post-operative outcomes in the adult population,

there remains an acute need for such a system in the paediatric population. The POSSUM (Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity) has been applied to a number of adult surgical groups including orthopaedic patients, vascular surgery, head and neck surgery and gastrointestinal/colorectal surgery (Copeland et al., 1991). Similarly, the Clavien-Dindo and Comprehensive Complication Index have been validated and successfully used in the adult population (Chapter 1).

Paediatric physiology scoring systems such as PELOD Score (Pediatric Logistic Organ Dysfunction), Paediatric Risk of Mortality (PRISM) score and the Paediatric Index of Mortality (PIM) are focussed on the acutely unwell paediatric patient in intensive care and calculates the mortality risk (Slater et al., 2003, Pollack et al., 1988, Leteurtre et al., 2003).

There is a need for an outcome predicting tool taking into account the post-operative complication which is designed specifically for the paediatric surgical population. The paediatric patient is unique and cannot be compared to a standard adult. Their physiology and therefore acute response to stress is different. The special group of complex paediatric patients have multiple factors affecting their post-operative outcome and should be taken into account. There is no score that takes into account the background conditions unique to much of the paediatric surgical population.

6.2 Aims of the study

My aim was to develop a Paediatric Complexity Index (PCI) that integrates the pre-operative complexity of paediatric patients with all post-operative events. The purpose of this tool is twofold. Firstly, to provide context related outcome measures to empower patients and parents to make informed choices and secondly, to serve as an appraisal tool for surgeons, while not

compromising those surgeons dealing with ‘complex’ child and to ‘prove’ a units performance.

6.3 Methods

I developed the PCI along with two paediatric surgical colleagues. Nine routinely recorded physiological and eight operative measures were taken into account. Factors were weighted so that severe co-morbidities score more heavily than multiple co-morbidities of lesser severity (Table 6-1). The weighting was done after a brainstorming session between three paediatric surgeons. It was then circulated, amended and agreed upon by all the Consultant paediatric surgeons in the department. In this study I did not use any muti-level modelling.

As a feasibility study I planned to run the PCI score on twenty patients. The project was registered with the hospital audit department (Registration number 1482). Ten patients with complex medical background and ten ‘non-complicated’ patients who underwent operations between January 2014 and September 2014 were scored using the PCI. These were compared with Comprehensive Complication Index (CCI) by linear regression analysis.

Patient complexity index, parameters	Parameter to review	Weighting (A + = >3, A = 2; B=1; C=0)
Number of previous operations at the same site (same scar for the same organ)	Number	
Nutritional status	Weight centile	A= <3 (malnourished) OR >50(obese); B= 3-25 /C=25-50 (ok)
Prematurity (0.5 points for IUGR)	<28, 28-32; 32-37	A+ = <28; A 28-32;B = 32-37; C=>37
Immunosuppression (any form = medical or chemical, steroids)	Yes or no	A=Yes; C=No
Unrelated site device/stoma: (e.g. central access +/- arterial line / long term vascular access device / gastrostomy or GJ or jejunostomy tube / CSF drainage device / tracheostomy / PD catheter / JJ stent) / stoma	Number	A + = >3, A = 2; B=1; C=0
Pre-operative Organ failure (acute / chronic) EXCLUDING CARDIAC		
ACUTE single / two organ / three or more	Number	A => 2; B=1; C=0
CHRONIC any site / number (GDD, Brain failure/ MSK/etc.)	Number	A=Yes; C=No
Age (years)	Number	A=0-1; B=1-12; C>12
PEWS score worst measured during anaesthesia Heart Rate BP Temp	PEWS Chart	 C = normal, A = tachy/bradycardia C = normal, A = hyper / hypotensive C = normal, A = hot/cold
Operation type Minor / intermediate / major/ complex major	As per Bupa classification	C, B, A, A+
Blood loss intra-operatively ml/kg of fluid/ blood products/ blood transfuse in theatre)	ml/kg 0-20; 20-50; 50-100; >100	C, B, A, A+
Deep space contamination	Yes or no	A=Yes; C=No
CEPOD status	Planned / expedited / urgent / immediate	C, B, A
ASA grade	I, II, III, IV, IV E (0.5 for E)	C, B, A, A+
Cardiac status	No cardiac failure history /corrected structural abnormality (e.g. PDA/ co-arctation of Aorta)/ uncorrected cardiac lesion or failure/ pulmonary hypertension	C, B, A, A+
Prosthesis > 2 weeks at this operation	Yes or no	A =Yes, C=No
Connective tissue disorder, epidermolysis syndromes = 1 extra point	Yes or no	B =Yes, C=No
Unplanned return to theatre within 1 week = 1 extra point	Yes or no	B =Yes, C=No

Table 6-1 Physiological and operative parameters used to calculate PCI

IUGR = Intra Uterine Growth Retardation, PEWS=Paediatric Early Warning Score, CEPOD= Confidential Enquiry into Peri-operative Deaths, ASA= American Society of Anesthesiologists, PDA=Patent Ductus Arteriosus

6.4 Results

Twenty patients were reviewed, ranging from age 0 days to fifteen years at time of operation (median 2.5 years). Ten patients had complex pre-operative status and underwent major operation while 10 patients were less complex and underwent intermediate operation (Table 6-2).

PCI correlated closely with CCI (R^2=0.54, p=0.0002, Figure 6-1). Several patients with physiologically abnormal parameters scored > 0 on PCI but 0 on CCI (i.e. no complications) highlighting that having a high PCI does not necessarily mean that they will have a complication but if they do have a complication then they are much more likely to have a high PCI.

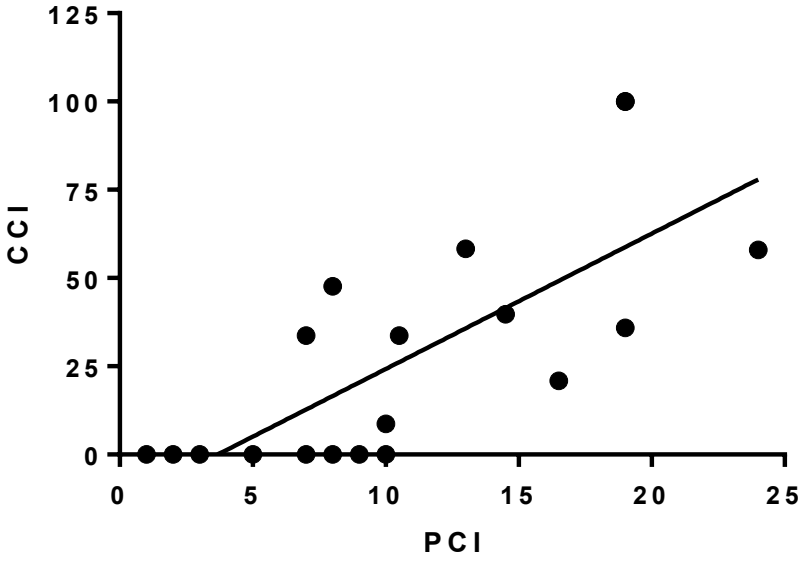


Figure 6-1 Linear regression analysis of CCI against PCI

R^2=0.54, p=0.0002

Complexity Index

Age	Operation	PCI	CCI
0.0	Ex 23 week gestation, TOF/OA, repaired, hickman line, NEC laparotomy, multi-organ failure	19	100
0.18	Ophthalmological operation, NEC post-op, laparotomy, wound dehiscence, stoma hernia	14.5	39.7
15.2	Intestinal dysmotility, stoma formation, multiple trips to theatre, prolonged stay +++	13	58.3
13.6	Crohns, fistula ++, multiple laparotomies	19	99.9
5.3	Trisomy 21, pulmonary hypertension, multiple admissions, gastro-oesophageal disconnection; roux loop needed lengthening	19	35.9
0.43	Obstruction post-Duhamel pull through needed return to theatre	8	47.7
0.51	Parastomal hernia in newly formed stoma, revised at laparotomy	10.5	33.7
0.12	Ex premature, NEC, loss of most of bowel	24	58
6.15	Ovarian tumour, return to theatre for bleeding	7	33.7
0.01	Pulmonary stenosis, NEC post-op requiring laparotomy	16.5	20.9
6.11	Closure of gastrostomy	9	0
0.19	Laparoscopic inguinal hernia repair	1	0
3.44	EUA anus + washout + revision anoplasty	7	0
1.05	Right orchidopexy	5	0
0.36	Laparoscopic inguinal hernia repair	10	0
1.5	Right branchial sinus excision	2	0
10.4	Roux en Y surgical jejunostomy	10	8.7
4.3	Removal of gastrostomy	8	0
3.4	Inguinal hernia repair, umbilical revision, insertion of grommet	3	0
9.7	(Crohn's) ileal stricture resection	8	0

Table 6-2 Patient characteristics, operation, PCI and CCI scores

6.5 Discussion

To maintain practical usability of the PCI it is important to include the factors most likely to have an effect on outcome, while not overcrowding and making the tool cumbersome. The PCI results from my pilot study are promising. However, it needs two-stage validation. The first is at the development stage. This can be done by enlisting a group of closely related physicians and surgeons (i.e. paediatric anaesthetists, paediatric intensivist and paediatric surgeons) to review the PCI parameters and their weighting. This cohort of assessors or the 'development cohort' can individually agree or disagree and remove or add further parameters. The result will then be compiled and the final PCI will be developed, by using appropriate mathematical formulae.

The second stage will be validation of the developed PCI. This can be achieved by the following methods:

1. *Prospectively* – Patients undergoing surgery will have their PCI calculated using the developed parameters. They will be reviewed until discharge or the first 30 days after the surgery, to determine complications. After 30 days the CCI will be calculated. The appropriate statistical analysis to test the ability of PCI to predict CCI will be undertaken. The advantage of this method is that selection bias is low, although it is time consuming and one needs to wait for the first 30 days to evaluate CCI.

2. *Retrospectively* – a cohort of patients who underwent surgery over a specified timescale can be analysed for their PCI and CCI. The appropriate statistical analysis can be applied to look at the relation of the two scores. This can be quicker to perform, however as the data is being collected retrospectively, there might be missing data leading to flawed result.

3. *Quality of Life validation* – A cohort of patients undergoing any operation can have their quality of life assessed by using the well validated EuroQol questionnaire EQ-5D (Brooks, 1996) at the time of discharge. The EQ-5D-Y (Wille et al., 2010) is designed for children and young adults. For the younger child, these can be filled in by the parents/carers. There would be expected to be a statistically significant negative correlation between PCI and the post-operative health status.

4. *Estimation of the severity of single vs. multiple comorbidity by conjoint analysis* – The weighting of the various factors can be tested by developing scenarios with single or multiple complications and asking parents to score on a visual analogue scale. The values of these scenarios' PCI can be calculated. These can be analysed using the principles of conjoint analysis (Bachmann et al., 2008).There should be a high positive correlation between the result of the conjoint analysis and the PCI.

6.5.1 Sample size

The sample size calculation of the validation cohort can be based on a pilot study, after there has been agreement at the 'development cohort' of the factors to include/exclude and their weightings. In addition, the sample size is very dependent on the scope of the proposed study (e.g. whether to include only patients having a post-operative overnight stay or also to include day surgery). The sample size should be able to detect a difference calculated from the pilot study and should have a power of 80% at a significance level of 0.05, and provision of a dropout rate of 15%.

6.5.2 Parent involvement

There has been an increased awareness and participation of parents in the decision making process for children's treatment. There are parents support

group for rare, complex conditions providing invaluable support to the affected families. We as surgeons have to work with them to ensure the best outcome for children.

In the adult health services Patient Reported Outcome Measures are increasingly being used for key elective operations. In children a similar initiative using parents are likely to become popular, but there are many complexities in their development.

6.6 Conclusions

Our preliminary data suggests that the PCI is an accurate tool to stratify patients with regards to pre- and intra-operative morbidity and therefore optimise patients at greater risk of complications, as well as make more sense of post-operative complications. It requires further development and extensive validation in a variety of patient groups but has the potential to allow accurate comparison of complications between different centres taking into account individual patient characteristics. We also need to develop a readily available, easily accessible and simple to use online tool so that this is widely reproducible.

I have had discussions with researchers involved in developing Patient Reported Outcome Measures at Oxford for adults. With their experience I hope this work can be taken forward to develop a similar model in children. This requires funding and pooling of resources from clinicians (paediatric anaesthetists, paediatric intensivist and paediatric surgeons) to non-clinicians such as health economists, psychologists, statisticians and website development specialist.

Chapter 7 General Discussion

Despite enteral feeding being the preferred mode of nutrition in the 'unwell' child, there is no consensus on the safest way to insert a gastrostomy, after a period of nasogastric tube feeding. There is considerable disagreement between gastroenterologists and paediatric surgeons and amongst paediatric surgeons themselves. There are advocates of the PEG, the RIG and the laparoscopic assisted gastrostomy. The two most common procedures performed at Great Ormond Street Hospital are PEG and RIG. In a retrospective study done at our institute, RIG was found to have more complications than PEG. This meant that ethically RIG should not be performed. However, there were drawbacks of the retrospective study in that the study population was not matched. In order to verify the results from the retrospective review, it was essential to perform a prospective randomised controlled trial.

In the research described in this thesis I have attempted to answer this question using one of the highest levels of evidence. The results of the trial showed that there is no difference between total number of complications or the rate of complications, following PEG or RIG. This has important impact on centres practising both the methods of gastrostomy insertion. It can lead to streamlining of patient treatment to the more readily available option without any concerns about difference in outcomes. Further study of this cohort of patients can provide information about the development of gastro-oesophageal reflux, need for further feeding device or resolution of symptoms and establishment of oral feeding. Further follow-up of these patients will indicate whether the equal efficacies of these procedures are still apparent at a later date.

While conducting the randomised controlled trial I was faced with ethical dilemmas with children in special circumstances such as social care, palliative care and with rare diseases. These circumstances along with the anatomy and physiology of these children make them unique and incomparable with adults.

I looked at the complications associated with a gastrostomy. The major complication of buried bumpers can sometimes be life threatening and at other times picked up as an incidental finding when the disc device is being changed to a balloon gastrostomy device. The incidence of this complication is not really known and reflects the reluctance to report it. I reviewed the literature and reviewed our own experience with gastrostomies over a 12-year period. This retrospective review was enhanced by undertaking a focussed telephonic interview to investigate care of the gastrostomy before and after the episode of buried bumper. The study showed that proper care and device maintenance are essential in preventing this complication. I also investigated the treatment options.

Children unable to tolerate gastric feeding, frequently as a result of gastro-oesophageal reflux, can have jejunal feeding. There is no long-term outcome study looking at the efficacy of jejunostomy feeding in children. The two commonly used methods at our institute are SJ and RGJ. The important aspect of any feeding method is the end result of ability to meet nutritional requirements and to maintain growth. I reviewed the complications and nutritional outcomes following jejunostomy placement (SJ or RGJ) at our institute. Both SJ and RGJ are able to maintain and improve growth in a carefully selected group of children, although SJ and RGJ cannot be compared as they are used for patients at different stages in a spectrum of malnutrition. Perhaps it will be more prudent to compare nutritional outcomes, complications and quality of life outcomes in a randomised controlled trial comparing RJ and anti reflux procedures. From a patient and carer perspective the ease of using the feeding device and its maintenance play an important part in their everyday life.

The reporting of complications after an operative procedure is not universal. There is either under reporting or no reporting at all. However, now with the Royal College of Surgeons making individual reporting of outcomes mandatory, the situation is likely to improve. The Clavien Dindo Grade followed by the more relevant Comprehensive Complication Index, are steps

towards transparent reporting of complication outcomes. However none of the available scoring systems take into account the background complexities specifically in children. I reviewed the available scoring systems for post-operative complications and developed a new paediatric complexity scoring system of risk stratification for post-operative complications. I have explored various validation strategies for the developed paediatric complexity scoring system. Impact of the complexity of paediatric patients on their post-operative complications needs thorough consideration to improve outcomes following their operation.

Chapter 8 Publications & Presentations arising from this Thesis

Publications

1. **A double blind randomised controlled trial of percutaneous endoscopic gastrostomy vs. radiologically inserted gastrostomy in children.**
   Rashmi R Singh, Shireen Nah, Derek J Roebuck, Simon Eaton, Agostino Pierro and Joe I Curry.
   British Journal of Surgery, 2017 Nov; 104(12): 1620-1627. doi: 10.1002/bjs.10687.

2. **Management of a Complication of Percutaneous Gastrostomy in Children.**
   Rashmi R Singh, Simon Eaton, Kate Cross, Joe I Curry, Paolo De Coppi, Edward M Kiely, Derek J Roebuck and Agostino Pierro.
   European Journal of Pediatric Surgery 2013 Feb; 23(1): 76-79

3. **Surgical Jejunostomy and radiological gastro-jejunostomy tube feeding in children: Risks, benefits and nutritional outcome.**
   Rashmi R Singh, Simon Eaton, Derek J Roebuck, Alex Barnacle, Samantha Chippington, Kate Cross, Paolo De Coppi and Joe I Curry.
   Pediatric Surgery International, 2018 Sep; 34(9): 951-956. doi: 10.1007/s00383-018-4303-8.

Presentations

British Association of Paediatric Surgeons (BAPS) Annual Congress

1. **A double blind randomised controlled trial of percutaneous endoscopic gastrostomy vs. radiologically inserted gastrostomy in children: PEG vs. RIG Trial.**
   Singh RR, Roebuck D, Barnacle A, Chippington A, Stuart S, Gibson C, Cross KMK, Stanwell J, Yardley IE, Kiely EM, DeCoppi P, Pierro A, Eaton S, Curry JI.
   Presented at Peter Paul Rickham and President's Prize session, Amsterdam 2016

2. **Jejunostomy feeding in children: Methods and nutritional outcome.**
   Singh RR, Eaton S, Macharia EW, Chippington S, Barnacle A, Pierro A, Cross KM, Kiely EM, Roebuck DJ, De Coppi P, Curry JI.
   Edinburgh, 2014

3. **Incidence and management of a complication of percutaneous gastrostomy.**
   Singh RR, Cross KM, Curry JI, De Coppi P, Kiely EM, Roebuck DJ, Pierro A.
   Rome, 2012

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Appendix 1 Trial Protocol

Version 4.0
Date: 15/03/2013

The PEG vs. RIG TRIAL

Percutaneous Endoscopic Gastrostomy versus

Radiologically Inserted Gastrostomy in Children

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1. Background

The use of gastrostomy tubes is a lifeline for long-term enteral nutrition in the pediatric patient in need of nutritional supplementation. Before 1980, the only method of gastrostomy insertion available was the open surgical technique. This is a relatively invasive procedure as it requires a separate formal surgical incision, and has been blamed for various adverse effects including precipitating gastroeosphageal reflux (1,2). It was Gauderer who first described his method of percutaneous endoscopic gastrostomy (PEG) in 1980 (3), which transformed the process by eliminating the need for a surgical wound. Since then, various minimally invasive techniques of gastrostomy insertion have been developed, including radiologically inserted gastrostomy (RIG) inserted under fluoroscopic guidance (4,5). Both methods of endoscopic and radiologically guided gastrostomy insertion have become established practice since they were first described nearly 3 decades ago

Gastrostomy insertion is a procedure commonly seen in children. Although there are a number of publications on both methods in the adult population (6,7,8), there is little information available in literature specifically comparing the 2 techniques in the pediatric population.

We carried out a review of 318 children who had either PEG or RIG insertion in our hospital between 2004 and 2008 (9). The conversion rate in the PEG group (8%) was higher than the RIG group (1%). This corresponds to a superior technical success rate of 97-100% reported in literature for the RIG technique (8,10-12). The majority of conversions were due to anatomical difficulties such as scoliosis and high position of the stomach with narrow subcostal angle, which are more likely to be present in neurologically impaired children.

Both PEG and RIG have the benefits of easy insertion and avoidance of laparotomy incision. However, both techniques are also associated with complications, including gastrocolic fistula, haemorrhage and intra-abdominal leak with sepsis (6,7,13,14).

In our study, the rate of major complications was low in both PEG and IG at 1% and 3% respectively (P=NS), which compared favourably to other reports (15-19). Patwardhan et al reported a 3.5% incidence of gastrocolic fistula in PEG over a 5 year period, a complication which was only seen in 1 PEG patient in our series (17). Other major complications have been described including placement of the catheter through a lobe of the liver, fistulation into the small bowel and 'buried bumper syndrome' (16,19,20,21).

We also reported that the overall number of patients who developed both major and minor complications were lower in PEG compared to RIG (28% vs 47%, P=0.001). This may have been due to the difference in case mix where more IG patients were immunocompromised to some degree due to chemotherapy for their underlying oncological illness. As reported by Barron et al, nearly half the patients in a series of pediatric hematology/oncology patients had localized tube site infection after IG insertion (19). In a study of late-onset complications of PEG in children by Segal et al, the overall rate of complications was 44% observed over a follow-up period of 1 to 8 years (22).

A direct comparison of complication rates can be inaccurate as the complications seen varied widely in severity. For instance, some published reports of minor complications took only wound site problems into account (19), while other reports also included delayed feeds and tube-related issues (11,12). In addition, some patients may experience more than a single complication. Thus, we devised a gastrostomy complication scoring system where complications were ascribed scores weighted for severity.

We believe that the total score per patient is a more accurate reflection of the success of the procedure.

One aspect of any surgical procedure that is becoming increasingly relevant today is a comparison of costs. Barkmeier et al indicated in their report that PEG was the less costly procedure (8). However, this advantage was lost when the need for operating theatre facilities and general anesthesia were factored in. Costs may also be further reduced with the use of primary gastrostomy button placements, reducing the number of tube changes required (23).

Given the lack of robust evidence that one method is superior to the other, we are proposing a randomised controlled trial to establish if PEG is better than RIG in outcome and complications.

2. Aims

The aim of this study is to demonstrate the most effective method of gastrostomy insertion in children. The hypothesis to be tested is that percutaneous endoscopic gastrostomy (PEG) is superior to radiologically inserted gastrostomy (RIG) in terms of outcome and complications.

3. Research Objectives

The proposed trial will define which technique is more effective: PEG or RIG.

The scientific reasons to justify such a trial are the following:

1. Gastrostomy insertion is a widely and frequently used procedure in children.
2. The ideal method of gastrostomy insertion is not known.

3. Both PEG and RIG can be associated with a number of complications (e.g. gastrocolic fistula, intra-abdominal leak with sepsis).

4. Methods

This will be a double blind single centre randomized controlled trial. 200 patients (100 in each arm) will be randomized to either PEG or RIG. Patients will be allocated to groups by weighted minimization (24). Minimization is a method of randomized treatment allocation, which ensures that the groups are balanced with respect to prognostic indicators (minimization criteria) that are likely to affect patient outcome. Minimization criteria used are detailed in Table 2.

The *inclusion criteria* for the study will be:

1. any child referred for gastrostomy insertion

The *exclusion criteria* for the trial are:

5. the child has gastro-esophageal reflux and is being considered for anti-reflux surgery
6. previous gastrostomy or fundoplication
7. previous extensive abdominal surgery
8. the child requires a concomitant major procedure on the gut or other intra-abdominal organs

Every referral for a gastrostomy will be assessed by the trial coordinator (Research Fellow) for the inclusion and exclusion criteria. If the exclusion criteria are absent, the parents or care giver of the referred child will be asked consent for inclusion in the trial and consequently for randomization. The patient will be randomized online using a fast and

simple method (or using the toss of a coin as back-up) to either PEG or RIG.

If the child is judged to be of suitable age and maturity, every attempt will be made to provide as much information as appropriate to the child regarding participation.

If consent for participation in the trial is refused, the parent or guardian will be approached for consent for data collection to continue even without participation in the trial. This data will also be analysed. They will also be invited for follow-up according to the trial schedule.

The *primary* end point of the study will be the total number of complications (major and minor).

The *secondary* end points of the study will be:

viii. major complication rate : colonic injury or gastrocolic fistula or other visceral injury, peritonitis requiring surgery, intestinal obstruction requiring surgery, major gastrointestinal bleed, other complications requiring surgery

ix. minor complication rate : infection requiring systemic antibiotics, delay more than 48 hours in establishing feeds, granulation, wound site discharge, tube-related problems (migration, dislodgement, leakage, breakage), other minor

x. complication score : this is a score devised with weighting assigned to each complication depending on the severity of the complication, as detailed in Table 1. The score was devised in a consensus meeting attended by experts in the field (paediatric surgeons, interventional radiologists, junior doctors and nurses.

	Type of complications		Score
Major complications	Colonic injury / gastrocolic fistula		20
	Peritonitis requiring surgery		20
	Intestinal obstruction requiring surgery		20
	Major gastrointestinal bleed	Requiring surgery	20
		Requiring transfusion but not surgery	10
	Buried Bumper		20
	Other complications requiring surgery		20
Minor complications	Infection requiring systemic antibiotics		1
	Delay more than 48 hours in establishing feeds		1
	Granulation		1
	Wound site discharge		1
	Tube-related problems	Migration	1
		Pulled out / dislodged	5
		Leakage around tube	2
		Breakage	2
	Other minor		2

Table 1: Gastrostomy scoring system for complications of gastrostomy insertion

xi. technical failure : these are the number of PEG or RIG that are unsuccessful and require conversion to open surgical gastrostomy or laparoscopic gastrostomy.

xii. difficulty of procedure : this will be assessed by the operator as : 1) easy, 2) slightly difficult (but does not warrant conversion 3) difficult (warrants conversion)

xiii. cost of hospital treatment

xiv. mortality

xv. cause of death

9. Randomisation

Patients will be allocated to groups by weighted minimization (23). Minimization is a method of randomized treatment allocation, which ensures that the groups are balanced with respect to prognostic indicators (minimization criteria) that are likely to affect patient outcome. Minimization criteria used will be the criteria laid out in Table 2.

Minimisation Criteria	**Definition**
Diagnosis	[Neurological] [Haematology/Oncology] [Metabolic] [Gastrointestinal Diseases] [Miscellaneous]
Age	[< 6months] [6 months – 2 years] [2 – 5 years] [>5 years]
Weight Centile	[<3%] [3-10%] [10-25%] [25-50%] [>50%]
Inpatient Status	[Yes] [No]
Scoliosis	[Yes] [No]
Gastro-esophageal reflux	[No] [Yes- Not needing anti-reflux surgery]

Table 2 : Minimisation Criteria

6. Statistics and Sample Size Estimation

For sample size estimation, we used a binary power calculation, i.e. proportion of patients with any complications in each group.

From our previous retrospective review of 318 children who had either PEG or RIG (9), 28% of PEG patients and 47% of RIG patients had complications.

To detect a difference of 19% (80% power, α=0.05), 100 patients per group are needed.

In our hospital, we perform a large number of gastrostomies per year (between 3-5 per week), and are confident that 200 patients in total will be recruited within 2 years.

Outcomes will be compared using appropriate regression analyses (linear, binary or Poisson), accounting for all the minimisation criteria. Data will be analysed on an intention to treat basis. We anticipate that with the trial powered for a binary outcome, we will have adequate power to examine outcomes using regression analyses.

The primary outcome will be analysed using zero-inflated Poisson regression analysis of complication score per patient over time. A zero-inflated Poisson distribution is expected on the basis of our retrospective review of complication scores in patients undergoing gastrostomy insertion.

7. Treatment Schedules

Procedures will be performed by consultant radiologists, gastroenterologists or paediatric surgeons; or by trainees at specialist registrar level under direct supervision by a consultant on site. All cases will be done under general anaesthesia with prophylactic antibiotics administered before the procedure. A 9 French silicone gastrostomy tube will be used.

The two standardized procedures compared in the trial are:

Percutaneous Endoscopic Gastrostomy

After insufflation of the stomach with an endoscope, indentation of the stomach and transillumination through the abdominal wall is confirmed

under endoscopic vision. A small incision is made over the area of maximum transillumination and a catheter mounted on a needle passed through followed by a guidewire (Seldinger technique). The guidewire is grasped by the endoscope, pulled out through the mouth and attached to the gastrostomy tube which is then pulled antegrade and out through the abdomen. The tube was is with an external fastener and no sutures were placed.

Radiologically Inserted Gastrostomy

This is done using biplane fluoroscopy, with pre-placement ultrasonography for localization of the liver. An orogastric snare is passed and the stomach punctured under fluoroscopic guidance with an 18-gauge needle which is used to insert a stiff 0.035-in guidewire. This is snared and withdrawn through the mouth. The snare catheter is introduced in a retrograde direction from the abdominal wall to the mouth, and the gastrostomy tube is grasped and pulled down the esophagus.

The stages of the study will be as follows:

Stage 1 – Enrolment

i) Patient is identified as eligible

ii) Consent is obtained from parent or guardian

iii) Demographics recorded and treatment randomized via internet

Stage 2 – Day of Procedure

Details of operative procedure (technical failure, difficulty of procedure, operator details)

Stage 3 – Postoperative period

Data is collected until discharge of the patient from hospital.

Stage 4 – Postoperative Follow-up

Patients are re-evaluated at 6 weeks **± 2 weeks**, 6 months**± 1 month**, 1 year **± 2 months** and 3 years **± 2 months** after the procedure. Complications are recorded and scored.

If by the time of evaluation, the participant has had the gastrostomy removed, and there is no clinical indication for follow-up, the evaluation will be done by remote interview (telephone or email).

8. Double Blind

The patient and parents or guardian will be blinded to the method of gastrostomy insertion used. The research nurse or research fellow assessing the complications will also be blinded.

9. Data Monitoring and Interim Analysis

Participants will be allocated a unique study number, and all study data will be stored with this number as the identifier. Identifiers will be held in a separate database. This separation will happen at the time of transcribing the data.

To ensure that the trial progress is in accordance with guidelines for good clinical practice in multicentre trials, the following Committees will be established:

1. Data Monitoring and Ethics Committee which will be independent of both the trial organisers and those providing therapy. This committee will perform interim analyses to: a) review assumptions underlying sample size considerations; b) modify or close intake to trial.

2. Trial Steering Committee which will include: i)independent Chairman (not involved in Trial); ii) two independent members (Paediatric Surgeon and Paediatrician); iii) nurse representative; iv) parents' representative; v) trial coordinators (AP, PDC and SE); vi) research fellow; vii) representative of the Data Monitoring and Ethics Committee. A statistician will attend meetings as appropriate. The role of this Committee is to provide overall supervision of the trial and ensure that the trial is conducted to rigorous scientific, clinical and ethical standards. It will particularly concentrate on progress of the trial, adherence to trial protocol, data collection and maximize the chances completion within the agreed time-table.

Data will be analysed at the Institute of Child Health and will be compared by appropriate parametric or non-parametric analyses. We will convene a Data Monitoring and Ethics Committee who will review the data when 100 patients have been recruited.
The criteria for stopping the trial will be defined as: (i) a significant difference ($p<0.01$) between the two arms overall complication rate; or (ii) significantly ($p<0.01$) greater incidence of major complications; in one arm compared to the other, analysed both as single outcomes and as total cumulative complications.

10. Compliance

In order to maximise compliance in the trial there will be a part time Research Fellow who will liaise with the clinical teams involved.
Confidentiality of data will be ensured.

11. Timetable

0-1 months: establish trial, complete Research Ethics Committee approvals, develop data management systems and databases; *2-24*

months: recruitment, randomisation and follow-up; *25-60 months:* Complete analyses, write final report for peer review publication.

12. Relevance

This trial addresses a fundamental question concerning the best management for children requiring gastrostomy insertion. This trial will establish which is the best procedure (i.e. PEG or RIG) in terms of outcome and associated complications.

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Appendix 2 Parent Information Sheet

PEG vs. RIG Trial
R&D No 10SG14
Version 2
Date: 15/03/2013

Parent Information Sheet

[Gastrostomy]

1. Study Title

PEG vs. RIG Trial

Percutaneous Endoscopic Gastrostomy versus

Radiologically Inserted Gastrostomy in children

2. Invitation Paragraph

You and your child have been invited to take part in a research study. Before you decide whether to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.
Thank you for reading this.

3. What is the purpose of the study?

You have been advised that your child requires a gastrostomy. A gastrostomy is a feeding device that is inserted through an opening in the abdomen to the stomach. This allows your child to be fed directly into his or her stomach, bypassing the mouth and throat.

People who have difficulties feeding can benefit from a gastrostomy. There are many reasons why someone might have difficulties feeding, including neurological (nervous system) disorders and gastrointestinal (digestive system) disorders. Some people also have difficulty swallowing, which increases the chance that they will breathe in food (aspirate).

Others who may benefit are those who are able to feed and swallow normally, but are unable to maintain an adequate intake for healthy weight gain. This usually occurs in times of severe illness, such as a child with cancer or leukaemia who is undergoing chemotherapy.

There are 2 common methods of inserting a gastrostomy under general anaesthesia:

1) Percutaneous endoscopic gastrostomy (PEG)
   This is inserted under the guidance of an endoscope (a flexible instrument with a camera at the end that is used to inspect the stomach). It is done by a gastroenterologist or paediatric surgeon.

2) Radiologically inserted gastrostomy (RIG)
   This is inserted under the guidance of radiological imaging, including ultrasound and video X-rays. It is done by a radiologist.

Both methods are widely used in many centres around the world, and are the 2 most common methods used in our hospital.

Despite the fact that both methods have been used for many years, we do not know which is better in terms of outcome and complications. This study will determine which method is the best.

4. Why have I been chosen?

Your child has been chosen because he/she requires a gastrostomy. The hospital and consultants taking part in the study are experienced in both operations and regularly perform both in children.

We are planning to recruit 200 children in this study.

5. Do I have to take part?

It is up to you to decide wether or not to take part. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care your child receives. ***Your child will still receive a gastrostomy which he/she requires anyway, but will not be part of the research.***

6. What will happen to my child if I take part?

Because we do not know which procedure is best for patients, we need to make comparisons. Children participating in this study will be put into one of two groups and then compared (randomised trial). The groups are selected using computer software which has no personal information about the individual – i.e. by chance. One group of children will then have the PEG and the other will have the RIG.

7. What do I have to do?

There will be no changes in the care to your child while he/she is participating in the study.

8. What is the procedure that is being tested?

Both procedures are being compared in this study.

9. What are the alternatives for treatment?

There are other methods of gastrostomy insertion but these are usually used when a PEG or RIG has been already inserted or when the surgeon anticipates some difficulty.

We believe that since your child has never had a gastrostomy inserted in the past, either PEG or RIG would be the most appropriate method.

10. What are the side effects of any treatment received when taking part?

Within the trial, your child will not receive any treatment other than the gastrostomy insertion. Your child will be closely monitored before and during the operation and on the ward after the operation.

All other care that your child would normally have will continue as usual.

There are no blood samples or any other samples that will be taken as part of the research.

11. What are the possible disadvantages and risks of taking part?

There are risks associated with all types of surgical procedures and your doctor will discuss these with you. There are no known disadvantages or risks for your child in taking part in this study over and above those risks that are associated with the procedures.

12. What are the possible benefits of taking part?

There is no intended clinical benefit to your child from taking part in the study. The information we get from this study may help us to improve the treatment of future children requiring a gastrostomy.

13. What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. A 'Data Monitoring Group', whose role it is to consider any such information will meet to determine what action, if any, is required. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue to have your child involved in the study. If you decide to withdraw, your research doctor will make arrangements for your child's care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information your research doctor might consider it in your child's best interest to withdraw them from the study. He/she will explain the reasons and arrange for your child's care to continue.

14. What happens when the research study stops?

We will monitor your child's progress for all the recovery times until discharge. Your GP will continue to monitor your child's progress as part of normal clinical care.

15. What if something goes wrong?

There are risks associated with all types of surgical procedure and your doctor will discuss these with you. Both operations have similar risks associated with them. The study has no known risks to your child over and above those risks that are associated with the surgery. However, research

can carry unforeseen risks and we want you to be informed of your rights in the unlikely event that any harm should occur as a result in taking part in this study.

The Institute of Child Health will provide no-fault compensation cover for its own staff involved in the trial. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

16. Will my taking part in this study be kept confidential?

All information which is collected about your child during the course of the research will be kept strictly confidential. Any information about your child which leaves the hospital will have his/her name and address removed so that he/she cannot be recognised from it. With your permission your GP or paediatrician will be notified of your child's participation in the study.

17. What will happen to the results of the research study?

The results of the study are likely to be published in medical journals. You can obtain a copy of the published results. Your child's name will not be identified in any report or publication.

18. Who is organising and funding the research?

Doctors at the Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust, London are organising this study. The study is being funded by Great Ormond Street Hospital Children's Charity. Patients will not be paid to participate in the study.

19. Contact for Further Information

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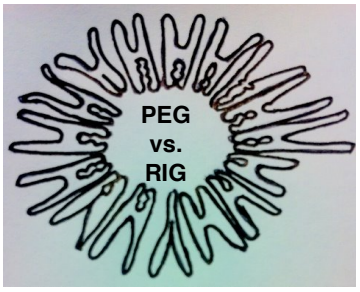
Thank you for considering taking part in this study.

Appendix 3 Data Collection Sheet



Outpatient / Telephonic follow-up (Please circle):

Patient Hospital Number _____

Patient Name _____

Post gastrostomy: (Please circle) 6 weeks, 6 months, 1 year, 3 years Removal at_____

Complication scores (Please circle):

Complications requiring surgery		**20**
Infection requiring systemic antibiotics		**1**
Delay more than 48 hours in establishing feeds		**1**
Granulation		**1**
Wound site discharge		**1**
Tube-related problems	**Migration**	**1**
	Pulled out / dislodged	**5**
	Leakage around tube	**2**
	Breakage	**2**
Other minor_____		**2**

If removed, why?_____

Any other concern_____

Appendix 4 DMEC Report

PEG vs. RIG Trial

Percutaneous Endoscopic Gastrostomy versus Radiologically Inserted Gastrostomy in Children

PEG vs. RIG Trial interim analysis

Data Monitoring and Ethics Committee

25th September 2013

Miss Rashmi R Singh

Clinical Research Fellow, UCL Institute of Child Health

Table of Contents

1. List of Tables

Page

2. List of Figures

Page

3. PEG vs. RIG Trial

3.1 Trial Details

Title - **Percutaneous Endoscopic Gastrostomy versus Radiologically Inserted Gastrostomy in Children**: Randomized Controlled Trial

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Registration Details

Registration	Reference	Date
R&D	10SG14	March 2010
National Research and Ethics	10/H0713/47	October 2010
Clinical Trials.gov Identifier	NCT01920438	August 2013

Trial Summary

Trial Start	November 2011
First Recruitment	November 2011
Trial End	September 2014

3.3 Introduction

Gastrostomy is the lifeline for many children with difficult or inadequate oral nutrition. It is usually performed in infants and children requiring short- to long- term enteral feeding. Neurologically impaired children with unco-ordinated and therefore unsafe swallow(Sleigh et al., 2004, Vernon-Roberts et al., 2010, Townsend et al., 2008); children undergoing or due to undergo intense chemotherapy resulting in intractable nausea and vomiting(Aquino et al., 1995, Schmitt et al., 2012, Pedersen et al., 1999, Mathew et al., 1996); children with metabolic disorders or renal failure requiring unpalatable medications or feeds in large volumes; children requiring a definite and secure means of enteral feed as a part of another surgical intervention (Urban and Terris, 1997, Al-Attar et al., 2012) and children with severe behavioral and gastrointestinal disorders have been greatly benefitted from this feeding device(Sathesh-Kumar et al., 2009, Nah et al., 2010).

Percutaneous endoscopic gastrostomy (PEG), and radiologically inserted percutaneous gastrostomy (RIG) have the benefits of easy insertion and avoidance of a laparotomy incision. However, both techniques are also associated with complications, including gastro-colic fistula, haemorrhage and intra-abdominal leak with sepsis (Cosentini et al., 1998, Vervloessem et al., 2009, Campos and Marchesini, 1999, Wollman et al., 1995). Although there are a number of publications on both methods in the adult population (Wollman et al., 1995, Cosentini et al., 1998, Barkmeier et al., 1998, Leeds et al., 2010, Blondet et al., 2010), there is little information available in literature specifically comparing the two techniques in the paediatric population.

3.4 Study Hypothesis

The aim of this study is to demonstrate the most effective method of gastrostomy insertion in children. The hypothesis to be tested is that percutaneous endoscopic gastrostomy (PEG) is superior to radiologically inserted gastrostomy (RIG) in terms of outcome and complications.

4 Data Monitoring and Ethics Committee (DMEC)

4.1 DMEC Composition

The Data Monitoring and Ethics Committee (DMEC) will be independent of both the trial organisers and those providing therapy. The members are listed below:

- Professor Lewis Spitz, Chairman
- Mr Niyi Ade-Ajayi, Member

4.2 DMEC Remit

The committee will perform interim analyses to:

1. Review assumptions underlying sample size considerations
2. Modify or close intake to trial

If there is overwhelming evidence of superiority of one treatment over the other the trial protocol recommends that the trial is stopped at this time. The trial stopping rules are described in full in table 1.

Table 1 Trial Stopping Rules

i. a significant difference ($p<0.01$) between the two arms overall complication rate; or ii. significantly ($p<0.01$) greater incidence of major complications; in one arm compared to the other, analysed both as single outcomes and as total cumulative complications .

5 Trial Process

This is a double blinded single centre randomised controlled trial. Two hundred patients (n = 100 in each arm) will be randomised to either PEG or RIG. Patients will be allocated to groups by weighted minimisation(Treasure and MacRae, 1998). The patient and parents or guardian will be *blinded* to the method of gastrostomy insertion used. The research nurse or research fellow assessing the complications will also be blinded.

Procedures will be performed by consultant radiologists, gastroenterologists or paediatric surgeons; or by trainees at specialist registrar level under direct supervision by a consultant on site. All cases will be done under general anaesthesia with prophylactic antibiotics administered before the procedure. A 9 French silicone gastrostomy tube will be used.

The two standardized procedures compared in the trial are:

Percutaneous Endoscopic Gastrostomy

After insufflation of the stomach with an endoscope, indentation of the stomach and transillumination through the abdominal wall is confirmed under endoscopic vision. A small incision is made over the area of maximum transillumination and a catheter mounted on a needle passed through followed by a guidewire (Seldinger technique). The guidewire is grasped by the endoscope, pulled out through the mouth and attached to the gastrostomy tube which is then pulled antegrade and out through the abdomen. The tube is fixed with an external fastener and no sutures placed.

Radiologically Inserted Gastrostomy

This is done using biplane fluoroscopy(Malden et al., 1992), with pre-placement ultrasonography for localization of the liver. An orogastric snare is passed and the stomach punctured under fluoroscopic guidance with an 18-gauge needle, which is used to insert a stiff 0.035-inch guidewire. This is snared and withdrawn through the mouth. The snare catheter is introduced in a retrograde direction from the abdominal wall to the mouth, and the gastrostomy tube is grasped and pulled down the esophagus.

5.1 Sample size

For sample size estimation, we used a binary power calculation, i.e. proportion of patients with any complications in each group.

From our previous retrospective review of 318 children who had either PEG or RIG(Nah et al., 2010) , 28% of PEG patients and 47% of RIG patients had complications.

To detect a difference of 19% (80% power, α=0.05), 100 patients per group are needed.

Outcomes will be compared using appropriate regression analyses (linear, binary or Poisson), accounting for all the minimisation criteria. Data will be analysed on an intention to treat basis. We anticipate that with the trial powered for a binary outcome, we will have adequate power to examine outcomes using regression analyses.

The primary outcome will be analysed using zero-inflated Poisson regression analysis of complication score per patient over time. A zero-inflated Poisson distribution is expected on the basis of our retrospective review of complication scores in patients undergoing gastrostomy insertion.

5.2 Inclusion Criteria

1. any child referred for gastrostomy insertion

5.3 Exclusion Criteria

1. the child has gastro-esophageal reflux and is being considered for anti-reflux surgery
2. previous gastrostomy or fundoplication
3. previous extensive abdominal surgery
4. the child requires a concomitant major procedure on the gut or other intra-abdominal organs

5.4 Randomisation and Minimisation Criteria

Each referral for a gastrostomy will be assessed for the inclusion and exclusion criteria. If the exclusion criteria are absent, the parents or care giver of the referred child will be asked consent for inclusion in the trial and consequently for randomisation. The patient will be randomised online using a fast and simple method (SiMin® software, developed by the Institute of Child Health, UCL) to either PEG or RIG.

Minimisation is a method of randomised treatment allocation, which ensures that the groups are balanced with respect to prognostic indicators (minimisation criteria) that are likely to affect patient outcome. This is based on the idea that the next patient to enter the trial is given whichever treatment would minimise the overall imbalance between the groups at that stage of the trial. Minimisation criteria used are detailed in Table 2.

Minimisation Criteria	**Definition**
Diagnosis	[Neurological] [Haematology/Oncology] [Metabolic] [Gastrointestinal Diseases] [Miscellaneous]
Age	[< 6months] [6 months – 2 years] [2 – 5 years] [>5 years]
Weight Centile	[<3%] [3-10%] [10-25%] [25-50%] [>50%]
Inpatient Status	[Yes] [No]
Scoliosis	[Yes] [No]
Gastro-esophageal reflux	[No] [Yes- Not needing anti-reflux surgery]

Table 2: Minimisation Criteria

5.5 Outcome Measures

The *primary* end point of the study will be the total number of complications (major and minor).

The *secondary* end points of the study will be:

i. major complication rate : colonic injury or gastro-colic fistula or other visceral injury, peritonitis requiring surgery, intestinal obstruction requiring surgery, major gastrointestinal bleed, other complications requiring surgery
ii. minor complication rate : infection requiring systemic antibiotics, delay more than 48 hours in establishing feeds, granulation, wound site discharge, tube-related problems (migration, dislodgement, leakage, breakage), other minor
iii. complication score : this is a score devised with weighting assigned to each complication depending on the severity of the complication, as detailed in Table 3. The score was devised in a consensus meeting attended by experts in the field (paediatric surgeons, interventional radiologists, junior doctors and nurses).

	Type of complications		Score
Major complications	Colonic injury / gastro-colic fistula		20
	Peritonitis requiring surgery		20
	Intestinal obstruction requiring surgery		20
	Major gastrointestinal bleed	Requiring surgery	20
		Requiring transfusion but not surgery	10
	Buried Bumper		20
	Other complications requiring surgery		20

Minor complications	Infection requiring systemic antibiotics		1
	Delay more than 48 hours in establishing feeds		1
	Granulation		1
	Wound site discharge		1
	Tube-related problems	Migration	1
		Pulled out / dislodged	5
		Leakage around tube	2
		Breakage	2
	Other minor		2

Table 3:Scoring system for complications of gastrostomy insertion

iv. technical failure : these are the number of PEG or RIG that are unsuccessful and require conversion to open surgical gastrostomy or laparoscopic gastrostomy.
v. difficulty of procedure : this will be assessed by the operator as : a) easy, b) slightly difficult (but does not warrant conversion) c) difficult (warrants conversion)
vi. cost of hospital treatment
vii. mortality
viii. cause of death

6 Results

6.1 Early Challenges

Ethical amendments were obtained to alter the original protocol in order to correct and clarify various details of the study, and also to include a follow-up window. These were approved by the ethics committee and by the R&D team. The recruitment began in November 2011.

The trial involves recruitment of patients needing a gastrostomy. These patients are under the care of various clinical teams including: General Surgery, Oncology, Haematology, Endocrine, Metabolic, Gastroenterology, and Nephrology. We organised departmental meetings and discussion with the clinicians involved in the care of the patients.

For the assessment at follow-up of the patients, we organised training of nurses in the Somers Clinical Research Facility.

Since then recruitment has progressed well. It has also sometimes been difficult to schedule patients for their procedure once recruited and allocated but now this process has been streamlined and runs effectively, so there is no delay in patients receiving a gastrostomy.

6.2 Patients Recruited

125 patients have been successfully recruited, over a period of 22 months. At this rate, I would expect to recruit the target of 200 patients by next year. The initial recruitment was slow due to the factors mentioned in the previous section. For the purpose of the DMEC the first 100 patients are being reviewed .

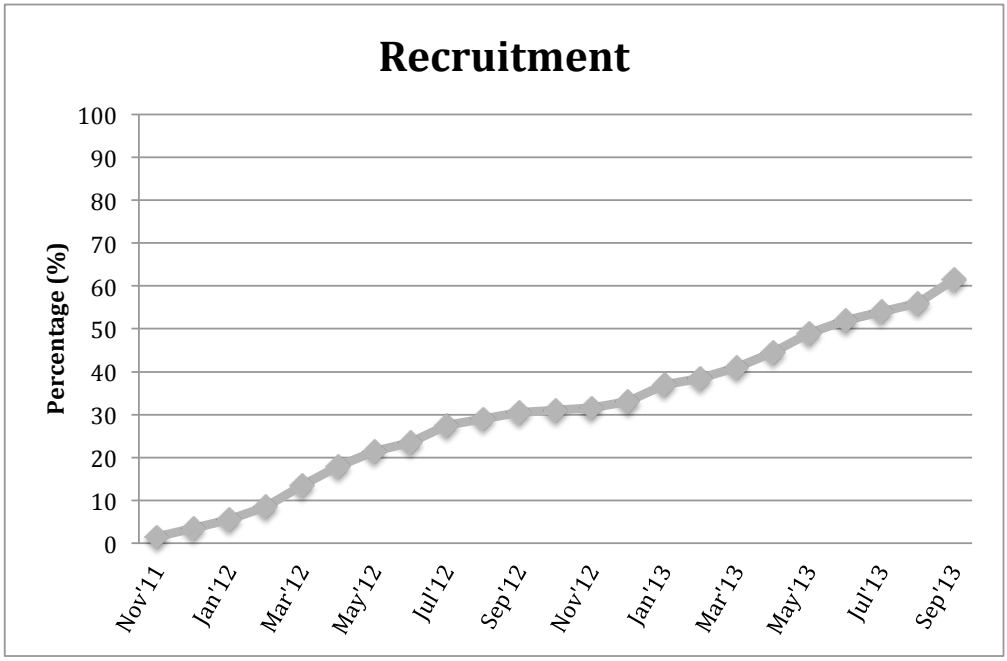

Figure 1: Chronological progress of patient recruitment.

6.3 Patient characteristics

This section describes the characteristics of the patients recruited so far. At interim review, the results of 100 patients were available for analysis.

	Categories	Group A	Group B	'p' value
1.	Diagnostic Group:			
	Neurological	15	13	
	Haem-oncological	12	13	
	Metabolic	6	7	
	Gastrointestinal	2	1	
	Other	16	15	0.5415*
2.	Age:			
	< 6 months	3	2	
	6 months- 2 years	21	21	
	2-5 years	14	9	
	> 5 years	13	17	0.8043*
3.	Weight centile:			
	<3%	16	16	
	3-10%	9	10	
	10-25%	7	4	
	25-50%	11	10	
	>50%	8	9	0.6213*
4.	Inpatient/Outpatient:			
	Inpatient	5	7	
	Outpatient	46	42	0.5501**
5.	Scoliosis:			
	Present	0	0	
	Absent	51	49	1**
6.	Gastro-oesophageal reflux:			
	Yes (controlled by medications)	14	8	
	No	37	41	0.2296**
	Group totals:	51	49	

* Paired t-test

** Fisher's exact test

Table 4: Patient Demographics and Clinical Characteristics

There is no significant difference in the baseline demographic and clinical characteristics between the two groups.

6.4 Acceptance Rate

In keeping with consort guidelines, we report our acceptance and recruitment to the trial, for the period of November 2011 to June 2013.

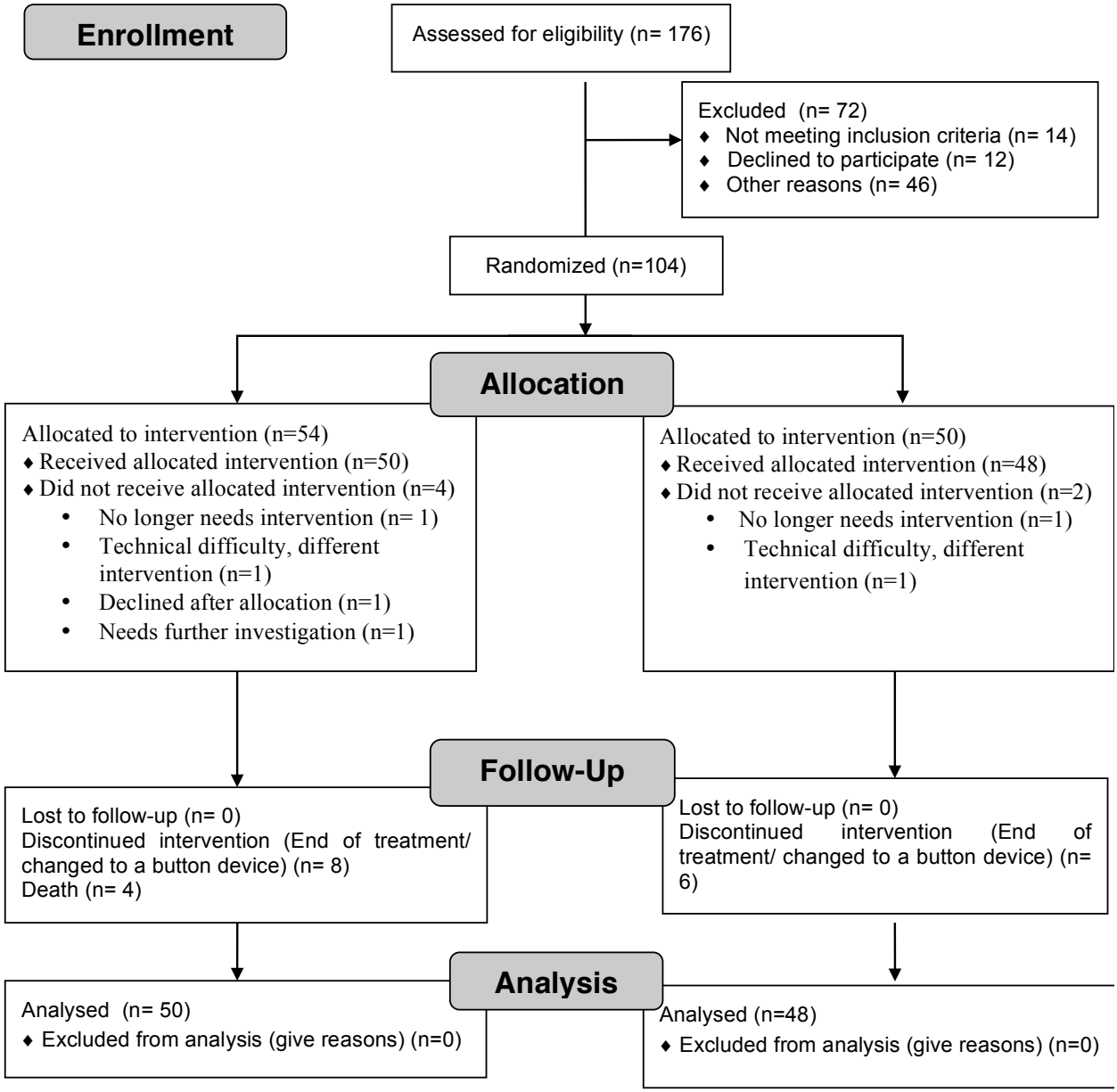

Figure 2: CONSORT flow diagram of recruitment for the period of November 2011 to June 2013

Seventy-two patients were not enrolled (using the CONSORT guideline (Moher et al., 2010) for reporting Figure 2, summarizes the progress). Fourteen patients were not eligible, 12 patients declined to participate in the study. Forty-six patients were excluded due to various reasons – intervention not needed, terminally ill patient requiring the intervention as a part of palliative treatment, patients from abroad (therefore, difficult to be followed up), patient requiring concomitant procedure, patients with neuro-muscular disorder following a specific pathway for treatment.

The 104 children enrolled were randomised to either PEG or RIG with weighted minimisation using the SiMin® software (Table 4). The median age at enrolment was 2.4 years (range 4 months to 16 years).

6.5 Outcomes

Patients are evaluated at 6 weeks ± 2 weeks,
6 months± 1 month,
1 year ± 2 months and
3 years ± 2 months after the procedure.

	6 weeks	6 months	1 year	Removed/Death
Group A	48	29	19	12
Group B	44	34	22	9

Table 5: Number of patients completing follow ups

Seven patients died before completing three years of follow-up due to their advanced primary oncological disease (4 in Group A and 3 in Group B). One patient has had a major complication needing a laparotomy after the intervention. The others have had complications ranging from none to a combination of minor complications.

	Group A	Group B
Primary end point: Total number of complications	80	79
Secondary end points:		
Major Complication	1	0
Minor Complication	79	79
Complication score at 6 weeks	78	70
Complication score at 6 months	31	29
Complication score at 1 year	20	25
Technical failure	1	1

Table 6: Primary and secondary end points

7. Conclusion

In summary, we believe the PEG vs. RIG trial is progressing well. Initial recruitment issues were addressed with amendments. There have been no serious and adverse events, and there is a detailed record keeping of any of these events (in keeping with ethical standards) were they to occur. The acceptance and follow up rate has been good with no loss to follow up recorded so far.

We hope that the DMEC will be satisfied with the trial progress until now and will encourage its completion.

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Appendix A: Serious Adverse Events

To date, there has been no serious adverse event among the cohort of participants randomised in the trial. The deaths (n=7) were not unexpected among patients with advanced haematological/oncological disease.

Months post procedure	Diagnosis
7 months	Medulloblastoma
2 months	Low grade glioma
13 months	Metastatic medulloblastoma
13 months	Cardiac rhabdomyosarcoma
6 months	ALL
5 months	Menke's disease, seizures,progressive neuropathy
5 months	AML, Pre BMT

Table 7: Characteristics of patients who died

(ALL = Acute Lymphoblastic Leukaemia, AML = Acute Myeloid Leukaemia, BMT = Bone Marrow Transplant)

Appendix B: Meeting Agenda

Data Monitoring and Ethics Committee Members

Professor Lewis Spitz

Mr Niyi Ade-Ajayi

STAT Trial Steering Committee

Mr Joe Curry

Dr Derek Roebuck

Dr Simon Eaton

Dr Paolo De Coppi

Miss Rashmi R Singh

Meeting Agenda

1. Introduction and Apologies
2. Apologies:
3. DMEC presentation
    a. Recruitment update
    b. Results update
    c. Protocol violations
    d. Serious Adverse Events
    e. Stopping rules
4. Any other Business
5. Plan Next meeting of DMEC

Appendix 5 Report of Serious Adverse Event